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UNITED STATES BANKRUPTCY COURT
SOUTHERN DISTRICT OF NEW YORK

In re:	**Chapter 11**
PURDUE PHARMA L.P., *et al.*,	**Case No. 19-23649 (RDD)**
Debtors.[1]	**(Jointly Administered)**

AMENDED DECLARATION OF TERRENCE RONAN IN SUPPORT OF MOTION OF DEBTORS FOR AUTHORIZATION TO ENTER INTO AMENDED AND RESTATED FUNDING AGREEMENT

[1] The Debtors in these cases, along with the last four digits of each Debtor's registration number in the applicable jurisdiction, are as follows: Purdue Pharma L.P. (7484), Purdue Pharma Inc. (7486), Purdue Transdermal Technologies L.P. (1868), Purdue Pharma Manufacturing L.P. (3821), Purdue Pharmaceuticals L.P. (0034), Imbrium Therapeutics L.P. (8810), Adlon Therapeutics L.P. (6745), Greenfield BioVentures L.P. (6150), Seven Seas Hill Corp. (4591), Ophir Green Corp. (4594), Purdue Pharma of Puerto Rico (3925), Avrio Health L.P. (4140), Purdue Pharmaceutical Products L.P. (3902), Purdue Neuroscience Company (4712), Nayatt Cove Lifescience Inc. (7805), Button Land L.P. (7502), Rhodes Associates L.P. (N/A), Paul Land Inc. (7425), Quidnick Land L.P. (7584), Rhodes Pharmaceuticals L.P. (6166), Rhodes Technologies (7143), UDF LP (0495), SVC Pharma LP (5717) and SVC Pharma Inc. (4014). The Debtors' corporate headquarters is located at One Stamford Forum, 201 Tresser Boulevard, Stamford, CT 06901.

I, Terrence Ronan, being fully sworn, hereby declare that the following is true to the best of my knowledge, information and belief:

1. I am an Executive Vice President and the Chief Financial Officer of Purdue Pharma L.P. ("**PPLP**" and, collectively with each of the other above-captioned debtors, the "**Debtors**," the "**Company**" or "**Purdue**"). I was employed by Purdue as Vice President of Finance on December 1, 2021 and became Executive Vice President and Chief Financial Officer on January 1, 2022. I have 30 years of finance experience in banking as well as corporate positions at the C-Suite level. Most recently I served as Executive Vice President and Chief Financial Officer of Atlantic Power Corporation, a publicly traded independent power producer, from 2012 until its sale in 2021. I am familiar with the day-to-day operations, business and financial affairs of the Debtors.

2. I submit this declaration (this "**Declaration**") in further support of the *Motion of Debtors for Authorization to Enter into Amended and Restated Funding Agreement* (the "**Motion**").[1] I am authorized to submit this Declaration on behalf of the Debtors.

3. Except as otherwise indicated, all facts set forth in this Declaration are based upon my personal knowledge, my review of relevant documents, information provided to me by other employees of the Company or my opinion based upon experience, knowledge and information concerning the operations of the Debtors and the pharmaceutical industry as a whole. If called upon to testify, I would testify competently to the facts set forth in this Declaration.

[1] Capitalized terms used and not otherwise defined herein have the meanings ascribed to them in the Motion.

4. According to the Centers for Disease Control and Prevention, there were over 75,000 deaths from opioid overdoses in the 12-month period ending in April 2021, up from approximately 56,000 the year before.[2]

5. Studies indicate that naloxone rescue medications are being dramatically underused by the American public.[3]

6. Intranasal naloxone is sold under the brand names Narcan® and Kloxxado™, among others. Studies indicate that the price of these products, which retail for $125 or more per twin pack,[4] creates a significant impediment to wider distribution, especially in communities hardest hit by the opioid crisis.[5] Generic versions of Narcan were launched in December of 2021.[6] The introduction of these products has not translated to a material reduction in price, as the generic formulations remain approximately 85% the price of Narcan and Kloxxado based on a review of recent data received by the Company from IQVIA National Sales Perspectives.

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[2] Centers for Disease Control and Prevention, Drug Overdose Deaths in the U.S. Top 100,000 Annually, https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/20211117.htm.

[3] *See* Lin, L., Brummett, C.M., Waljee, J.F. et al., Association of Opioid Overdose Risk Factors and Naloxone Prescribing in US Adults, J. Gen. Intern. Med. 35, 420–427 (2020), https://doi.org/10.1007/s11606-019-05423-7 (concluding with respect to naloxone prescriptions that, "overall prescribing remains minimal. Additional efforts are needed across health systems to increase naloxone prescribing for patients at risk for opioid overdose.").

[4] Drugs.com, Narcan Nasal Spray Prices, Coupons and Patient Assistance Programs, https://www.drugs.com/price-guide/narcan-nasal-spray.

[5] *See* Gupta, R. et al. The rising price of naloxone — risks to efforts to stem overdose deaths, N. Engl. J. Med. 2016; 375:2213-2215, https://www.nejm.org/doi/full/10.1056/NEJMp1609578.

[6] Teva Pharmaceutical Industries Limited, Teva Announces Launch of First-to-Market Generic Version of Narcan® (Naloxone Hydrochloride Nasal Spray), in the U.S. (December 22, 2021), https://www.tevapharm.com/news-and-media/latest-news/teva-announces-launch-of-first-to-market-generic-version-of-narcan-naloxone-hydrochloride-nasal-spray/; Sandoz, Sandoz launches authorized generic of Narcan® (naloxone hydrochloride) Nasal Spray 4 mg in US to help reverse opioid overdose, expanding access during surge in overdose deaths (December 22, 2021), https://www.us.sandoz.com/news/media-releases/sandoz-launches-authorized-generic-narcan-naloxone-hydrochloride-nasal-spray-4#:~:text=Princeton%2C%20New%20Jersey%2C%20December%2022%2C%202021%20%E2%80%94%20Sandoz%2C,US%20via%20retail%20pharmacies%20and%20institutions%2C%20including%20hospitals.

7. Intranasal naloxone is a prescription medication, though states have enacted legislation or issued standing orders enabling its sale without a prescription.[7] However, studies indicate that even these standing orders impose barriers to access, including requiring individuals to request (sometimes with concerns of stigma) the medication from a pharmacist.[8] One recent study found that making an OTC naloxone product available could result in a "substantial increase" in naloxone pharmacy sales, potentially as high as 179%.[9] If availability of OTC naloxone reduces the rate of fatal overdoses by just a few percentage points, thousands of lives could be saved every year.[10]

[7] SAFEProject, State Naloxone Access Rules and Resources, https://www.safeproject.us/naloxone-awareness-project/state-rules/.

[8] *E.g.,* Murphy, S. et al., *Will Converting Naloxone to Over-the-Counter Status Increase Pharmacy Sales?* Health Services Research, 2019; Vol. 54, No. 4, pp. 764–772, 771 ("[M]oving naloxone to OTC would help normalize the purchasing process, and likely reduce concerns of stigma by customers, which would also serve to increase demand."). In addition, even in states that have increased access to naloxone via retail pharmacies, not all pharmacies stock and dispense naloxone, implying that there is unmet demand. *See* Guadamuz, J. et al., *Availability and Cost of Naloxone Nasal Spray at Pharmacies in Philadelphia, Pennsylvania, 2017*, J. Am. Med. Assoc. 2019, Vol. 2, No. 6, e195388 (Two years after statewide Pennsylvania standing order came into effect, 34.2% of pharmacies surveyed in Philadelphia had naloxone nasal spray in stock; of these, 61.5% indicated it was available without a prescription); Puzantian, T. et al., *Provision of Naloxone without a Prescription by California Pharmacists 2 Years After Legislation Implementation*, 2018, Vol. J. Am. Med. Assoc. 1933, 1933–1934 (Two years after California standing order was enacted, pharmacist-furnished naloxone was available at 23.5% of pharmacies sampled); Meyerson, B. et al., *Predicting Pharmacy Naloxone Stocking and Dispensing Following a Statewide Standing Order, Indiana 2016*, Drug and Alcohol Dependence, 2018, Vol. 188, pp. 187–192 (One year after the standing order came into effect in Indiana, just over half (58.1%) of pharmacies stocked naloxone, and only 23.6% of pharmacists dispensed it).

[9] Murphy et al., *supra* note 9 at 770.

[10] Estimates from three widely cited empirical studies can be used to calculate the impact of naloxone availability on overdose survival rates. Together, these studies indicate that approximately 250 naloxone kits need to be distributed in order to avert one overdose death. Coffin, P. O. and S. D. Sullivan, *Cost-effectiveness of Distributing Naloxone to Heroin Users for Lay Overdose Reversal*, Annals of Internal Med., Vol. 158, No. 1, 1–9 (Jan. 2013); Walley, A. Y. et al., *Opioid Overdose Rates and Implementation of Overdose Education and Nasal Naloxone Distribution in Massachusetts: Interrupted Time Series Analysis*, BMJ, 1–13 (Jan. 2013); National EMS Information System, *Public Naloxone Administration Dashboard*, available at https://nemsis.org/view-reports/public-reports/version-3-public-dashboards/public-naloxone-administration-dashboard/.

8. The FDA has been actively encouraging drug companies to increase access to naloxone by developing an OTC product.[11] For example, in January of 2019, the FDA announced that it had developed a model Drug Facts label, which is required for OTC drug products, for both a nasal spray and an autoinjector device, and that the FDA had itself conducted the comprehensive testing that drug companies normally must complete to demonstrate that the instructions on the label are simple to follow.[12] This marks the first time that the FDA has ever proactively developed and tested a Drug Facts label for a drug to support development of an OTC product. The FDA stated that it took this extraordinary step because some potential entrants identified the label design and testing process as a barrier to development.[13]

9. The American Medical Association likewise strongly supports improved access to naloxone. On February 15, 2022, the AMA published a letter to the U.S. Surgeon General urging "removing the prescription status of naloxone as an essential step to save lives from opioid-related overdose because it will help make naloxone more readily available to patients everywhere."[14]

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[11] *See, e.g.*, U.S. Food and Drug Admin., FDA Statement, *Statement from FDA Commissioner Scott Gottlieb, M.D., on agency's efforts to advance new ways to increase the availability of naloxone as one means for reducing opioid overdose deaths* (Oct. 23, 2018), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-efforts-advance-new-ways-increase-availability; U.S. Food and Drug Admin., FDA Statement, *Statement from FDA Commissioner Scott Gottlieb, M.D., on unprecedented new efforts to support development of over-the-counter naloxone to help reduce opioid overdose deaths* (Jan. 17, 2019), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-unprecedented-new-efforts-support-development-over; U.S. Food and Drug Admin., FDA Statement, *Statement on continued efforts to increase availability of all forms of naloxone to help reduce opioid overdose deaths* (Sept. 20, 2019), https://www.fda.gov/news-events/press-announcements/statement-continued-efforts-increase-availability-all-forms-naloxone-help-reduce-opioid-overdose.

[12] U.S. Food and Drug Admin., FDA Statement, *Statement from FDA Commissioner Scott Gottlieb, M.D., on unprecedented new efforts to support development of over-the-counter naloxone to help reduce opioid overdose deaths* (Jan. 17, 2019), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-unprecedented-new-efforts-support-development-over; *see also* Cohen, B. et al., *FDA Initiative for Drug Facts Label for Over-the-Counter Naloxone*, N. Engl. J. Med. 2020; 382:2129-2136, https://www.nejm.org/doi/pdf/10.1056/NEJMsa1912403?listPDF=true.

[13] Cohen, B. et al., *FDA Initiative for Drug Facts Label for Over-the-Counter Naloxone*, N. Engl. J. Med. 2020; 382:2129–2136.

[14] Madara, J.L., Am. Med. Ass'n, *Letter to the Honorable Rahul Gupta, MD, Director, White House Office of National Drug Control Policy* (Feb. 15, 2022), https://searchlf.ama-

This statement is the most recent of many from the AMA calling for OTC naloxone.[15] In addition, numerous media sources have reported on the need for improved access to naloxone overdose reversal drugs.[16]

10. HRT is the only organization known by the Debtors to be responding to the FDA's call for an OTC naloxone nasal spray device. The Debtors have been HRT's only source of financial support since September of 2018. In August of 2018, HRT submitted an initial $3.5 million grant application to Purdue's Office of Corporate Social Responsibility ("**CSR**"). Upon review, CSR considered the amounts that would be required to contribute to development and FDA submission, and recommended approval of a $3.42 million grant. CSR weighed a number of factors, both positive and negative, when conducting its review, including that the request was in line with helping to address the opioid crisis with no expectation of remuneration or financial gain, the need for OTC naloxone and the attendant benefit to enabling HRT to begin work without further delay, the risk that HRT's product might not ultimately be approved, and the risk associated with the need for HRT to raise additional future investment. After receiving the requisite internal approvals, PPLP made this initial $3.42 million unrestricted grant in September 2018. PPLP

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assn.org/letter/documentDownload?uri=%2Funstructured%2Fbinary%2Fletter%2FLETTERS%2F2022-2-15-Letter-to-Gupta-re-ONDCP-Naloxone.pdf.

[15] *E.g.*, Madara, J.L., Am. Med. Ass'n, *Letter to Emergent BioSolutions* (Nov. 4, 2021), https://searchlf.ama-assn.org/letter/documentDownload?uri=%2Funstructured%2Fbinary%2Fletter%2FLETTERS%2F2021-11-4-Emergent-BioSolutions-FINAL.pdf; Am. Med. Ass'n, AMA Statement, *AMA: FDA action on OTC naloxone will save people from overdoses* (Jan. 17, 2019), https://www.ama-assn.org/press-center/ama-statements/ama-fda-action-otc-naloxone-will-save-people-overdoses ("As called for by AMA policy and ongoing advocacy, today's action should spur efforts by naloxone manufacturers to submit applications for their products to receive over-the-counter status. Doing so would be an important step to save even more lives from a national epidemic.").

[16] *E.g.*, Pattani, Aneri, *To Save Lives, Overdose Antidote Should Be Sold Over-the-Counter, Advocates Argue*, NPR (Dec. 14, 2021); Lee, Jacquie, *Naloxone Dispensing Is Way Up, but Some Areas Still Lag Behind*, BLOOMBERG LAW (Nov. 26, 2019); Gerencher, Kristen, *FDA Urges Broader Access to Naloxone to Avoid Opioid Overdose Deaths*, FORBES (Sept. 25, 2019); Court, Emma, *130 Americans Die Each Day from Opioid Overdoses. Experts Are Asking Why a Lifesaving Treatment Isn't Widely Available Without a Prescription*, BUSINESS INSIDER (Sept. 23, 2019).

funded an additional $2.5 million in the ordinary course for further development of the Product in November 2019. In return, HRT affirmed its commitment to manufacture millions of units of RiVive so that such units can be donated free of charge or sold at Cost (as defined in the A&R Agreement). In June 2020, PPLP funded an additional $6.5 million pursuant to that certain Funding Agreement, dated as of June 25, 2020, by and between PPLP and HRT (the "**2020 Funding Agreement**"). For the avoidance of doubt, Purdue has only made the three grants to HRT described in this paragraph, in the aggregate amount of $12.42 million. The Debtors understand that HRT has been unable to obtain financing from other third parties.

11. HRT's management team has a long and successful history transitioning prescription medications to OTC. Members of the management team have helped develop OTC versions of products such as Nicorette®, Plan B®, Nasacort® Allergy, NicoDerm® CQ®, Prilosec OTC® and Allegra®, among others. Members of the team also have deep expertise in addiction research and substance abuse treatment.

12. HRT possesses a proprietary preservative-free 3 mg naloxone formulation that is well suited to intranasal delivery. To date, with the Debtors' financial and technical support, HRT has developed an intranasal naloxone formulation, received conditional FDA approval for the RiVive trade name, completed a successful clinical trial demonstrating that its intranasal naloxone formulation is comparable to the FDA approved comparator, established scientific and advisory boards and identified key vendors, including a contract manufacturer and a sales and distribution vendor. HRT has also conducted Chemistry, Manufacturing, and Control and formulation work and begun to prepare the Product's NDA. The device that will deliver RiVive is field-tested, with over 25 years of FDA approvals for administration of, among other medicines, Narcan, migraine medications, anti-epilepsy medications and vitamin B12 applications. In practical terms, the

Debtors believe that HRT is well positioned for final FDA review and approval of the RiVive NDA by the end of 2023 or early 2024.

13. The Milestone Events and associated Milestone Payments in the Agreement are:

Milestone Event and Primary Purpose	Milestone Payment	Expected Milestone Achievement/ Expected Payment Date
Clinical study successfully demonstrates that RiVive naloxone concentrations are as high as the FDA approved comparator product (Development, drug product stability, NDA preparation, device reliability and production equipment)	$3,000,000	Completion date: January 31, 2022. Milestone achieved. Payment Due Date: April 1, 2022
Acceptable drug product 24-month stability achieved to support targeted 24-month shelf life for commercial product (NDA preparation, pre-validation batch manufacture, sales & marketing preparations and on-going development work)	$3,000,000	Targeted completion date: August 31, 2022 Payment Due Date: Within thirty (30) days after HRT delivers a written notice to PPLP that the applicable milestone has been met
New Drug Application for RiVive filed with the FDA (Manufacturing site readiness, partial support of commercial batch components, sales and marketing support prior to 1st commercial shipment)	$5,000,000	Targeted completion date: October 28th, 2022 Payment Due Date: Within thirty (30) days after HRT delivers a written notice to PPLP that the applicable milestone has been met

14. HRT's funding request is supported by, among other things, a detailed budget and development timeline.

15. Without the First Milestone Payment, HRT currently projects that it would exhaust all funds on hand by the end of April.

16. Further delay of the development timeline could substantially delay the launch of a life-saving medication. For instance, the Debtors understand that if HRT were to stop work on the 24-month drug stability program the entire program would have to be restarted from the beginning,

likely resulting in the termination of the project, or at minimum a 2-3 year delay before HRT could file an NDA with the FDA.

17. To the extent that HRT satisfies a Milestone Event and the Debtors make a Milestone Payment under the A&R Agreement, such Milestone Payment would be applied against the PHI Budget.

18. The Debtors' Board of Directors approved the Debtors' entry into the Agreement.

19. The negotiation of the terms of the Agreement was conducted at arm's length.

20. Upon the Debtors' careful consideration of the Agreement, including the benefits and risks attendant thereto, I believe that the relief requested in the Motion is in the best interests of all stakeholders in these Chapter 11 Cases.

[Remainder of Page Intentionally Left Blank]

Dated: March 2, 2022
New York, New York

By: */s/ Terrence Ronan*
Terrence Ronan
Executive Vice President and
Chief Financial Officer
Purdue Pharma L.P.

Appendix I

1. Centers for Disease Control and Prevention, Drug Overdose Deaths in the U.S. Top 100,000 Annually, https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/20211117.htm.

2. *See* Lin, L., Brummett, C.M., Waljee, J.F. et al., Association of Opioid Overdose Risk Factors and Naloxone Prescribing in US Adults, J. Gen. Intern. Med. 35, 420–427 (2020), https://doi.org/10.1007/s11606-019-05423-7.

3. Drugs.com, Narcan Nasal Spray Prices, Coupons and Patient Assistance Programs, https://www.drugs.com/price-guide/narcan-nasal-spray.

4. *See* Gupta, R. et al. The rising price of naloxone — risks to efforts to stem overdose deaths, N. Engl. J. Med. 2016; 375:2213-2215, https://www.nejm.org/doi/full/10.1056/NEJMp1609578.

5. Teva Pharmaceutical Industries Limited, Teva Announces Launch of First-to-Market Generic Version of Narcan® (Naloxone Hydrochloride Nasal Spray), in the U.S. (December 22, 2021), https://www.tevapharm.com/news-and-media/latest-news/teva-announces-launch-of-first-to-market-generic-version-of-narcan-naloxone-hydrochloride-nasal-spray/.

6. Sandoz, Sandoz launches authorized generic of Narcan® (naloxone hydrochloride) Nasal Spray 4 mg in US to help reverse opioid overdose, expanding access during surge in overdose deaths (December 22, 2021), https://www.us.sandoz.com/news/media-releases/sandoz-launches-authorized-generic-narcan-naloxone-hydrochloride-nasal-spray-4#:~:text=Princeton%2C%20New%20Jersey%2C%20December%2022%2C%202021%20%E2%80%94%20Sandoz%2C,US%20via%20retail%20pharmacies%20and%20institutions%2C%20including%20hospitals.

7. SAFEProject, State Naloxone Access Rules and Resources, https://www.safeproject.us/naloxone-awareness-project/state-rules/.

8. Murphy, S. et al., *Will Converting Naloxone to Over-the-Counter Status Increase Pharmacy Sales?* Health Services Research, 2019; Vol. 54, No. 4, pp. 764–772, 771.

9. Guadamuz, J. et al., *Availability and Cost of Naloxone Nasal Spray at Pharmacies in Philadelphia, Pennsylvania, 2017*, J. Am. Med. Assoc. 2019, Vol. 2, No. 6, e195388.

10. Puzantian, T. et al., *Provision of Naloxone without a Prescription by California Pharmacists 2 Years After Legislation Implementation*, 2018, Vol. J. Am. Med. Assoc. 1933, 1933–1934.

11. Meyerson, B. et al., *Predicting Pharmacy Naloxone Stocking and Dispensing Following a Statewide Standing Order, Indiana 2016*, Drug and Alcohol Dependence, 2018, Vol. 188, pp. 187–192.

12. Coffin, P. O. and S. D. Sullivan, *Cost-effectiveness of Distributing Naloxone to Heroin Users for Lay Overdose Reversal*, Annals of Internal Med., Vol. 158, No. 1, 1–9 (Jan. 2013).

13. Walley, A. Y. et al., *Opioid Overdose Rates and Implementation of Overdose Education and Nasal Naloxone Distribution in Massachusetts: Interrupted Time Series Analysis*, BMJ, 1–13 (Jan. 2013).

14. National EMS Information System, *Public Naloxone Administration Dashboard*, available at https://nemsis.org/view-reports/public-reports/version-3-public-dashboards/public-naloxone-administration-dashboard/.

15. U.S. Food and Drug Admin., FDA Statement, *Statement from FDA Commissioner Scott Gottlieb, M.D., on agency's efforts to advance new ways to increase the availability of naloxone as one means for reducing opioid overdose deaths* (Oct. 23, 2018), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-efforts-advance-new-ways-increase-availability.

16. U.S. Food and Drug Admin., FDA Statement, *Statement from FDA Commissioner Scott Gottlieb, M.D., on unprecedented new efforts to support development of over-the-counter naloxone to help reduce opioid overdose deaths* (Jan. 17, 2019), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-unprecedented-new-efforts-support-development-over.

17. U.S. Food and Drug Admin., FDA Statement, *Statement on continued efforts to increase availability of all forms of naloxone to help reduce opioid overdose deaths* (Sept. 20, 2019), https://www.fda.gov/news-events/press-announcements/statement-continued-efforts-increase-availability-all-forms-naloxone-help-reduce-opioid-overdose.

18. Cohen, B. et al., *FDA Initiative for Drug Facts Label for Over-the-Counter Naloxone*, N. Engl. J. Med. 2020; 382:2129–2136.

19. Madara, J.L., Am. Med. Ass'n, *Letter to the Honorable Rahul Gupta, MD, Director, White House Office of National Drug Control Policy* (Feb. 15, 2022), https://searchlf.ama-assn.org/letter/documentDownload?uri=%2Funstructured%2Fbinary%2Fletter%2FLETTERS%2F2022-2-15-Letter-to-Gupta-re-ONDCP-Naloxone.pdf.

20. Madara, J.L., Am. Med. Ass'n, *Letter to Emergent BioSolutions* (Nov. 4, 2021), https://searchlf.ama-assn.org/letter/documentDownload?uri=%2Funstructured%2Fbinary%2Fletter%2FLETTERS%2F2021-11-4-Emergent-BioSolutions-FINAL.pdf.

21. Am. Med. Ass'n, AMA Statement, *AMA: FDA action on OTC naloxone will save people from overdoses* (Jan. 17, 2019), https://www.ama-assn.org/press-center/ama-statements/ama-fda-action-otc-naloxone-will-save-people-overdoses.

22. Pattani, Aneri, *To Save Lives, Overdose Antidote Should Be Sold Over-the-Counter, Advocates Argue*, NPR (Dec. 14, 2021).

23. Lee, Jacquie, *Naloxone Dispensing Is Way Up, but Some Areas Still Lag Behind*, BLOOMBERG LAW (Nov. 26, 2019).

24. Gerencher, Kristen, *FDA Urges Broader Access to Naloxone to Avoid Opioid Overdose Deaths*, FORBES (Sept. 25, 2019)

25. Court, Emma, *130 Americans Die Each Day from Opioid Overdoses. Experts Are Asking Why a Lifesaving Treatment Isn't Widely Available Without a Prescription*, BUSINESS INSIDER (Sept. 23, 2019).

Appendix I-1

Centers for Disease Control and Prevention

Drug Overdose Deaths in the U.S. Top 100,000 Annually

For Immediate Release: November 17, 2021

Contact: CDC, National Center for Health Statistics, Office of Communication (301) 458-4800
E-mail: paoquery@cdc.gov

Provisional data from CDC's National Center for Health Statistics indicate that there were an estimated 100,306 drug overdose deaths in the United States during 12-month period ending in April 2021, an increase of 28.5% from the 78,056 deaths during the same period the year before.

The new data documents that estimated overdose deaths from opioids increased to 75,673 in the 12-month period ending in April 2021, up from 56,064 the year before. Overdose deaths from synthetic opioids (primarily fentanyl) and psychostimulants such as methamphetamine also increased in the 12-month period ending in April 2021. Cocaine deaths also increased, as did deaths from natural and semi-synthetic opioids (such as prescription pain medication).

The provisional data presented in this visualization include: the reported and predicted (estimated) provisional counts of deaths due to drug overdose occurring nationally and in each jurisdiction; a U.S. map of the percentage changes in provisional drug overdose deaths for the current 12-month ending period compared with the 12-month period ending in the same month of the previous year, by jurisdiction; and the reported and predicted provisional counts of drug overdose deaths involving specific drugs or drug classes occurring nationally and in selected jurisdictions.

The reported and predicted provisional counts represent the numbers of deaths due to drug overdose occurring in the 12-month periods ending in the month indicated. These counts include all seasons of the year and are insensitive to variations by seasonality. Deaths are reported by the jurisdiction in which the death occurred.

The interactive web dashboard is available at: https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm.

Page last reviewed: November 17, 2021

Appendix I-2

Original Research | Published: 09 December 2019

Association of Opioid Overdose Risk Factors and Naloxone Prescribing in US Adults

Lewei (Allison) Lin M.D., M.S., Chad M. Brummett M.D., Jennifer F. Waljee M.D., M.P.H., M.S., Michael J. Englesbe M.D., Vidhya Gunaseelan M.B.A., M.S., M.H.A. & Amy S. B. Bohnert Ph.D., M.H.S.

Journal of General Internal Medicine **35**, 420–427(2020) | Cite this article

Abstract

Background

Prescribing naloxone to patients is a key strategy to prevent opioid overdoses, but little is known about the reach of naloxone prescribing.

Objective

Determine patient factors associated with receiving naloxone and trends over time in patients with key overdose risk factors.

Design

Retrospective observational study.

Participants

Using the Clinformatics DataMart, a US-wide health insurance claims dataset, we compared adults who received opioids and naloxone (opioid+naloxone) from January 2014 to June 2017 with adults who received opioids without naloxone (opioids only), matched on gender, age ± 5 years, month/year of opioid fill, and number of opioid claims.

Main Measures

Key patient-level opioid overdose risk factors included receipt of high-dosage opioids, concurrent benzodiazepines, history of opioid and other substance use disorders, and history of opioid overdose.

Results

We included 3963 opioid+naloxone and 19,815 opioid only patients. Key factors associated with naloxone fills included high opioid daily dosage (50 to < 90 morphine milligram equivalents (MME): AOR = 2.43, 95% CI 2.15–2.76 and ≥ 90 MME: AOR = 3.94, 95% CI 3.47–4.46; reference: < 50 MME), receiving concurrent benzodiazepines (AOR = 1.27, 95% CI 1.16–1.38), and having a diagnosis of opioid use disorder (AOR = 1.56, 95% CI 1.40–1.73). History of opioid overdose was not associated with naloxone (AOR = 0.92, 95% CI 0.74–1.15). The percent of patients receiving naloxone increased, yet less than 2% of patients in any of the key overdose risk factor groups received naloxone by the last 6 months of the study period.

Conclusions

Naloxone prescribing has increased and was more likely to be co-prescribed to patients with some risk factors for overdose. However, overall prescribing remains minimal. Additional efforts are needed across health systems to increase naloxone prescribing for patients at risk for opioid overdose.

Appendix I-3

Drugs.com
Know more. Be sure.

Narcan Nasal Spray Prices, Coupons and Patient Assistance Programs

Narcan Nasal Spray (naloxone) is a member of the antidotes drug class and is commonly used for Opioid Overdose, and Reversal of Opioid Sedation.

Narcan Nasal Spray Prices

The cost for Narcan Nasal Spray nasal spray (4 mg/0.1 mL) is around $140 for a supply of 2 spray, depending on the pharmacy you visit. Prices are for cash paying customers only and are not valid with insurance plans.

A generic version of Narcan Nasal Spray is available, see naloxone prices.

This Narcan Nasal Spray price guide is based on using the Drugs.com discount card which is accepted at most U.S. pharmacies.

Nasal Spray

4 mg/0.1 mL Narcan Nasal Spray nasal spray
from **$140.00** for 2 spray

Quantity	Per unit	Price
2	$70.00	$140.00

Important: When there is a range of pricing, consumers should normally expect to pay the lower price. However, due to stock shortages and other unknown variables we cannot provide any guarantee.

Narcan Nasal Spray Coupons and Rebates

Narcan Nasal Spray offers may be in the form of a printable coupon, rebate, savings card, trial offer, or free samples. Some offers may be printed right from a website, others require registration, completing a questionnaire, or obtaining a sample from the doctor's office.

There are currently no Manufacturer Promotions that we know about for this drug.

Patient Assistance Programs for Narcan Nasal Spray

Patient assistance programs (PAPs) are usually sponsored by pharmaceutical companies and provide free or discounted medicines to low income or uninsured and under-insured people who meet specific guidelines. Eligibility requirements vary for each program.

There are currently no Patient Assistance Programs that we know about for this drug.

Appendix I-4

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

DECEMBER 8, 2016

The Rising Price of Naloxone — Risks to Efforts to Stem Overdose Deaths

Ravi Gupta, B.S., Nilay D. Shah, Ph.D., and Joseph S. Ross, M.D., M.H.S.

The Food and Drug Administration (FDA) first approved naloxone in 1971 as an injection (Narcan) for reversing opioid intoxication or overdose. Although the brand-name version has been discontinued, generic versions of naloxone have been available since 1985, and today injections are available in two doses (0.4 mg per milliliter and 1 mg per milliliter; see table). In 2014, the FDA fast-tracked approval of the first auto-injector formulation (Evzio), a fixed-dose single injection designed to allow people without medical training to reverse opioid overdose. In 2015, the agency fast-tracked approval of the first nasal-spray formulation (also marketed as Narcan); previously, naloxone injections (larger vials of a 1-mg-per-milliliter dose) had routinely been used off-label with an atomizer for nasal delivery.

In 2013, more than 80% of naloxone use was for heroin overdose, although there were twice as many deaths from prescription-opioid overdose as from heroin overdose.[1] Several U.S. federal agencies have therefore recommended increasing access to naloxone, particularly for prescription-opioid users. The Substance Abuse and Mental Health Services Administration developed an overdose-prevention tool kit in 2013, advising clinicians to coprescribe naloxone to patients taking opioids after considering a variety of factors, including whether these patients were receiving long-term or high-dose opioid therapy.

In 2015, the Department of Health and Human Services published its priorities in combating opioid overdoses, including accelerating development of new naloxone formulations and user-friendly products and expanding naloxone utilization by disbursing grants to states for naloxone-purchasing programs. Earlier this year, the Centers for Disease Control and Prevention (CDC) recommended that clinicians coprescribe naloxone to patients taking opioids and concurrently using benzodiazepines, patients taking higher opioid dosages (≥50 morphine milligram equivalents per day), and patients with a history of overdose or substance use disorder. The 2016 Comprehensive Addiction and Recovery Act builds on these guidelines and calls for additional grants to expand access to naloxone — by means of provider training and drug purchasing, for instance.

Similarly, some states have increasingly pursued initiatives designed to improve access to naloxone. Historically, it has been illegal for physicians to prescribe naloxone to third parties, such as family members or friends of patients at risk for overdose. One new approach, adopted by 40 states so far, is to offer clinicians various

Recent and Current Prices for Naloxone.*

Naloxone Product	Manufacturer	Previous Available Price (yr)	Current Price (2016)
Injectable or intranasal, 1 mg-per-milliliter vial (2 ml) (mucosal atomizer device separate)	Amphastar	$20.34 (2009)	$39.60
Injectable			
0.4 mg-per-milliliter vial (10 ml)	Hospira	$62.29 (2012)	$142.49
0.4 mg-per-milliliter vial (1 ml)	Mylan	$23.72 (2014)	$23.72
0.4 mg-per-milliliter vial (1 ml)	West-Ward	$20.40 (2015)	$20.40
Auto-injector, two-pack of single-use prefilled auto-injectors (Evzio)	Kaleo (approved 2014)	$690.00 (2014)	$4,500.00
Nasal spray, two-pack of single-use intranasal devices (Narcan)	Adapt (approved 2015)	$150.00 (2015)	$150.00

* Price information was obtained from Medi-Span Price Rx (Wolters Kluwer Clinical Drug Information).

levels of immunity from criminal or civil prosecution for third-party prescriptions. Laws in 42 states also grant criminal or civil immunity to bystanders who possess or use illegal drugs when they provide emergency services to someone who has overdosed, including administering naloxone or calling emergency responders.

A second strategy has been to allow people without a prescription to obtain naloxone at pharmacies through physicians' standing orders, collaborative practice agreements, or pharmacists' prescriptive authority; this approach has been authorized in 40 states, up from 1 in 2012. All told, the number of states with at least one law expanding access to naloxone increased from 8 in 2012 to 46 in 2016.

Beyond legislation, a rapidly growing number of community organizations now provide naloxone kits and education programs to laypersons,[1] and states and partnering agencies are doing the same with emergency medical services (EMS) providers.

Given the attention focused on naloxone and the initiatives broadening recommendations for its use, one would expect rapid increases in utilization. But between 2009 and 2015, the annual number of naloxone prescriptions increased only from 2.8 million to 3.2 million; while retail-prescription numbers were unchanged, the proportion attributed to clinics and EMS providers has grown from 14% to 29%.[2] The relatively slow adoption of naloxone may be due in large part to stigmatization and lack of familiarity with the treatment among clinicians and opioid users.[3] Another reason, however, may be its rising cost, which is probably enabled by the small number of manufacturers producing it.

Each formulation of naloxone — two injection doses, Narcan nasal spray, and Evzio auto-injector — essentially has one supplier. Though there are three manufacturers with FDA approval for 0.4-mg-per-milliliter-dose injections, the vast majority are sold by Hospira, which has increased the price by 129% since 2012 (see table). Only Amphastar manufactures 1-mg-per-milliliter injections, the dose used off-label as a nasal spray, which currently costs $39.60 after a 95% increase in September 2014. Newer, easier-to-use formulations are even more expensive. Narcan costs $150 for two nasal-spray doses. A two-dose Evzio package was priced at $690 in 2014 but is $4,500 today, a price increase of more than 500% in just over 2 years.

Naloxone's price increase is part of an overall trend of increasing prescription-drug prices for both new brand-name drugs and old, off-patent generics. Public frustration with rising drug prices has led to a number of recent policy proposals, including Vermont's new legislation requiring companies to justify price increases, California's attempt to constrain drug payments, and the recently proposed and bipartisan-supported Fair Accountability and Innovative Research Drug Pricing Act. None of the federal or state initiatives expanding naloxone's availability, however, address the drug's rising cost.

We believe that such policies should explicitly call on manufacturers to reduce the price of naloxone and increase transparency regarding their costs, particularly those related to the development of new formulations. For example, Evzio's price jumped significantly and without explanation the month before the CDC's coprescription guidelines were released. Several U.S. senators — most recently, Susan Collins

(R-ME) and Claire McCaskill (D-MO) — have sent letters asking naloxone manufacturers to explain their price increases. Though these requests recall recent investigations into Mylan, the manufacturer of the EpiPen, the naloxone situation has not garnered the type of attention or outrage inspired by that case, perhaps in part because of the stigma associated with opioid use.

There are additional steps governments could take to address naloxone's price increase. First, naloxone could be purchased in bulk, which would create stable demand that might motivate additional companies to begin manufacturing the medication — a strategy that's been used for vaccine manufacturing. Second, governments could invoke federal law 28 U.S.C. section 1498 to contract with a manufacturer to act on behalf of the United States and produce less costly versions of Evzio's patented auto-injector in exchange for reasonable royalties — an approach that was considered for procuring ciprofloxacin during the anthrax threat in 2001.[4] Third, in response to increases in generic drug prices, some observers have proposed allowing importation of generics from international manufacturers that have received approval from regulators with standards comparable to those of the FDA,[5] a strategy that could be pursued for naloxone.

In the long term, the FDA could also offer incentives to additional companies to obtain approval to market generic versions of naloxone by prioritizing more timely approval and waiving application user fees, which may require congressional action but would probably stimulate price competition. In the past, the FDA has discussed switching naloxone to over-the-counter status,[2] a conversation that could be revisited given the expected benefits for patient access. The relative ease of receiving FDA authorization for over-the-counter medications would also probably attract additional manufacturers.

Naloxone coprescribing and expanded availability represents only one of many potential strategies for reducing the number of prescription-opioid and heroin overdose deaths in the United States. But when governments promote naloxone use, they have a responsibility to ensure the drug's affordability. Taking action now is essential to ensuring that this lifesaving drug is available to patients and communities.

Disclosure forms provided by the authors are available at NEJM.org.

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DOI: 10.1056/NEJMp1609578

All-Payer Claims Databases — Uses and Expanded Prospects after *Gobeille*

John D. Freedman, M.D., M.B.A., Linda Green, M.P.A., and Bruce E. Landon, M.D., M.B.A.

Health care spending is approaching 20% of the U.S. gross domestic product, yet spending on research to improve the functioning of the health care system has been limited. What is worse, we generally lack a unified source of data to study all persons and the services they receive. Medicare data are national in scope but are limited primarily to people over age 65 and are not representative of behaviors or spending for the commercially insured.[1] Furthermore, since Medicare's prices are set administratively, its data cannot be used to study issues such as market power and competition. Data from commercial health insurers are limited because each plan represents only a portion of the market and enrollees frequently change plans.

To address these gaps, 16 states have established all-payer claims databases (APCDs), which gather health insurance eligibility, provider, and claims data, including payment information, from virtually all payers in a state to create

Appendix I-5

Teva Announces Launch of First-to-Market Generic Version of Narcan® (Naloxone Hydrochloride Nasal Spray), in the U.S.

DECEMBER 22, 2021

TEL AVIV, Israel & PARSIPPANY, N.J.--(BUSINESS WIRE)-- Teva Pharmaceuticals, a U.S. affiliate of Teva Pharmaceutical Industries Ltd. (NYSE and TASE: TEVA), today announced the launch of a first-to-market generic version of Narcan®[1] (naloxone hydrochloride nasal spray), in the United States.

Naloxone hydrochloride nasal spray is a prescription medicine used for the treatment of an opioid emergency such as an overdose or a possible opioid overdose with signs of breathing problems and severe sleepiness or not being able to respond.

With nearly 550 generic medicines available, Teva has the largest portfolio of FDA-approved generic products on the market, and holds the leading position in first-to-file opportunities, with approximately 100 pending first-to-files in the U.S. Currently, 1 in 12 generic prescriptions dispensed in the U.S. is filled with a Teva generic product.

What is naloxone hydrochloride nasal spray?

- Naloxone hydrochloride nasal spray is a prescription medicine used for the treatment of an opioid emergency such as an overdose or a possible opioid overdose with signs of breathing problems and severe sleepiness or not being able to respond.
- Naloxone hydrochloride nasal spray is to be given right away and does not take the place of emergency medical care. Get emergency medical help right away after giving the first dose of naloxone hydrochloride nasal spray, even if the person wakes up.
- Naloxone hydrochloride nasal spray is safe and effective in children for known or suspected opioid overdose.

IMPORTANT SAFETY INFORMATION

What is the most important information I should know about naloxone hydrochloride nasal spray?
Naloxone hydrochloride nasal spray is used to temporarily reverse the effects of opioid medicines. The medicine in naloxone hydrochloride nasal spray has no effect in people who are not taking opioid medicines. Always carry naloxone hydrochloride nasal spray with you in case of an opioid emergency.

1. Use naloxone hydrochloride nasal spray right away if you or your caregiver think signs or symptoms of an opioid emergency are present, even if you are not sure, because an opioid emergency can cause severe injury or death. Signs and symptoms of an opioid emergency may include:
   - unusual sleepiness and you are not able to awaken the person with a loud voice or by rubbing firmly on the middle of their chest (sternum)
   - breathing problems including slow or shallow breathing in someone difficult to awaken or who looks like they are not breathing

- the black circle in the center of the colored part of the eye (pupil) is very small, sometimes called "pinpoint pupils," in someone difficult to awaken

2. Family members, caregivers, or other people who may have to use naloxone hydrochloride nasal spray in an opioid emergency should know where naloxone hydrochloride nasal spray is stored and how to give naloxone hydrochloride before an opioid emergency happens.
3. **Get emergency medical help right away after giving the first dose of naloxone hydrochloride nasal spray.** Rescue breathing or CPR (cardiopulmonary resuscitation) may be given while waiting for emergency medical help.
4. The signs and symptoms of an opioid emergency can return after naloxone hydrochloride nasal spray is given. If this happens, give another dose after 2 to 3 minutes using a new naloxone hydrochloride nasal spray and watch the person closely until emergency help is received.

Who should not use naloxone hydrochloride nasal spray?
Do not use naloxone hydrochloride nasal spray if you are allergic to naloxone hydrochloride or any of the ingredients in naloxone hydrochloride nasal spray. See the end of the Patient Information Leaflet found at the end of the Prescribing Information for a complete list of ingredients in naloxone hydrochloride nasal spray.

What should I tell my healthcare provider before using naloxone hydrochloride nasal spray?
Before using naloxone hydrochloride nasal spray, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems
- are pregnant or plan to become pregnant. Use of naloxone hydrochloride nasal spray may cause withdrawal symptoms in your unborn baby. Your unborn baby should be examined by a healthcare provider right away after you use naloxone hydrochloride nasal spray.
- are breastfeeding or plan to breastfeed. It is not known if naloxone hydrochloride passes into your breast milk.

Tell your healthcare provider about the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

What are the possible side effects of naloxone hydrochloride nasal spray?
Naloxone hydrochloride nasal spray may cause serious side effects, including:

- **Sudden opioid withdrawal symptoms.** In someone who has been using opioids regularly, opioid withdrawal symptoms can happen suddenly after receiving naloxone hydrochloride nasal spray and may include: body aches, diarrhea, increased heart rate, fever, runny nose, sneezing, goose bumps, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, stomach cramping, weakness, or increased blood pressure.

In infants under 4 weeks old who have been receiving opioids regularly, sudden opioid withdrawal may be life-threatening if not treated the right way. Signs and symptoms include: seizures, crying more than usual, and increased reflexes.

These are not all of the possible side effects of naloxone hydrochloride nasal spray. Call your doctor for medical advice about side effects. You are encouraged to report side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch (https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.fda.gov%2Fmedwatch%2520or%2520call%25201-800-FDA-1088&esheet=52555111&newsitemid=20211222005564&lan=en-US&anchor=www.fda.gov%2Fmedwatch&index=1&md5=b22b237f245c41c791be05ec0f396d4d) or call 1-800-FDA-1088.

Please read the Patient Information Leaflet in the full Prescribing Information (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.tevagenerics.com%2Fglobalassets%2Fproducts%2Fpi%2Fnaloxone-hcl-nasal-spray_pi.pdf&esheet=52555111&newsitemid=20211222005564&lan=en-US&anchor=Prescribing+Information&index=2&md5=3ae078144da24bbfa71874aa868d7022).

About Teva

Teva Pharmaceutical Industries Ltd. (NYSE and TASE: TEVA) has been developing and producing medicines to improve people's lives for more than a century. We are a global leader in generic and specialty medicines with a portfolio consisting of over 3,500 products in nearly every therapeutic area. Around 200 million people around the world take a Teva medicine every day, and are served by one of the largest and most complex supply chains in the pharmaceutical industry. Along with our established presence in generics, we have significant innovative research and operations supporting our growing portfolio of specialty and biopharmaceutical products. Learn more at www.tevapharm.com (https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.tevapharm.com&esheet=52555111&newsitemid=20211222005564&lan=en-US&anchor=www.tevapharm.com&index=3&md5=3c2acdc765dc27c061462f1b84c6e318).

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, which are based on management's current beliefs and expectations and are subject to substantial risks and uncertainties, both known and unknown, that could cause our future results, performance or achievements to differ significantly from that expressed or implied by such forward-looking statements. You can identify these forward-looking statements by the use of words such as "should," "expect," "anticipate," "estimate," "target," "may," "project," "guidance," "intend," "plan," "believe" and other words and terms of similar meaning and expression in connection with any discussion of future operating or financial performance. Important factors that could cause or contribute to such differences include risks relating to the development, approval and commercialization of our generic products; our ability to successfully compete in the marketplace, including: that we are substantially dependent on our generic products, consolidation of our customer base and commercial alliances among our customers, delays in launches of new generic products, the increase in the number of competitors targeting generic opportunities and seeking U.S. market exclusivity for generic versions of significant products, our ability to develop and commercialize additional pharmaceutical products, and the effectiveness of our patents and other measures to protect our intellectual property rights; our substantial indebtedness; our business and operations in general, including uncertainty regarding the COVID-19 pandemic and its impact on our business, financial condition, operations, cash flows, and liquidity and on the economy in general; our ability to successfully execute and maintain the activities and efforts related to the measures we have taken or may take in response to the COVID-19 pandemic and associated costs therewith; costs and delays resulting from the extensive pharmaceutical regulation to which we are subject or delays in governmental processing time due to travel and work restrictions caused by the COVID-19 pandemic; the effects of reforms in healthcare regulation and reductions in pharmaceutical pricing, reimbursement and coverage; significant sales to a limited number of customers; our ability to successfully bid for suitable acquisition targets or licensing opportunities, or to consummate and integrate acquisitions; and our prospects and opportunities for growth if we sell assets; compliance, regulatory and litigation matters, including failure to comply with complex legal and regulatory environments; other financial and economic risks; and other factors discussed in our Annual Report on Form 10-K for the year ended December 31, 2020, including in the section captioned "Risk Factors." Forward-looking statements speak only as of the date on which they are made, and we assume no obligation to update or revise any forward-looking statements or other information contained herein, whether as a result of new information, future events or otherwise. You are cautioned not to put undue reliance on these forward-looking statements.

[1] Narcan® is a registered trademark of Emergent Operations Ireland Limited.

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Source: Teva Pharmaceutical Industries Limited

Appendix I-6

SANDOZ A Novartis Division

Sandoz launches authorized generic of Narcan® (naloxone hydrochloride) Nasal Spray 4 mg in US to help reverse opioid overdose, expanding access during surge in overdose deaths

Back to News Archive (https://www.us.sandoz.com/news/news-archive)

Dec 22, 2021

- *Opioid overdoses accounted for more than 73,000 deaths in US in one year (through April 2021) based on Center for Disease Control and Prevention's latest provisional data*[1]
- *Opioid overdose deaths increased almost 40 percent during COVID-19 pandemic (June 2019 vs May 2020),*[2] *highlighting need for more people to have access to overdose-reversing medicine during evolving national crisis*
- *Sandoz is committed to help ensure crucial generic medicines are available at affordable prices to those who need them*

Princeton, New Jersey, December 22, 2021 — Sandoz, a global leader in generic and biosimilar medicines, today announced the US launch of its authorized generic of Narcan®(naloxone hydrochloride)* Nasal Spray 4mg, which is used to reverse opioid overdose.[3] It is immediately available to people in the US via retail pharmacies and institutions, including hospitals.

Approximately every 8 minutes in the US a life is lost to an opioid overdose.[4] Opioid dependency and accidental opioid overdoses are a serious national crisis affecting public health and social and economic welfare. Opioid overdose death rates have been continuously increasing in the US for over two decades.[5]

During the COVID-19 pandemic, increased stressors such as isolation, unemployment and illness -- along with disruptions in health care and obstacles obtaining treatment -- have put people at increased risk of opioid overdose.[6] Of the 49 million patients prescribed opioids in the US, more than 18 million are considered at-risk, but only five percent received a prescription for naloxone.[7]

“Now more than ever, it’s imperative that Americans have increased access to life-saving opioid overdose reversal medicines for themselves or a loved one,” said Keren Haruvi, President, Sandoz Inc. “The launch of our authorized generic of Narcan® Nasal Spray reinforces our commitment to delivering high-quality, affordable generic medicines and to do our part to help address the public health epidemic for people at risk for opioid overdose.”

In July 2020, the US Food and Drug Administration (FDA) issued recommendations to healthcare professionals (HCPs) encouraging them to discuss the availability of naloxone with patients at increased risk of opioid overdose, which includes certain patients taking opioid pain relievers or medicines to treat opioid use disorder.[8] FDA has also identified situations in which an HCP may give strong consideration to prescribing naloxone, e.g., for patients prescribed medications for opioid use disorder or if the patient’s household has members at risk for accidental opioid ingestion or overdose.[9]

All 50 states in the US allow for access to the 4 mg naloxone hydrochloride nasal spray either directly from a pharmacist without a prescription under a Statewide Standing Order, a Collaborative Practice Agreement between pharmacists and other health care providers or through a third-party prescription that allows someone other than the patient to obtain the 4 mg naloxone hydrochloride nasal spray to assist an at risk individual.[10] Family and friends are often in the best position to administer this potentially lifesaving drug to those who overdose. State laws vary for eligibility and distribution.[11]

To learn more about the Sandoz naloxone hydrochloride authorized generic, visit www.sandoz-naloxone.com (http://www.sandoz-naloxone.com/) .

*Narcan is a registered trademark of Emergent Operation Ireland Limited.

INDICATION AND USAGE

Naloxone HCl Nasal Spray is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. Naloxone HCl Nasal Spray is intended for immediate administration as emergency therapy in settings where opioids may be present. Naloxone HCl Nasal Spray is not a substitute for emergency medical care.

IMPORTANT SAFETY INFORMATION

Naloxone HCl Nasal Spray is contraindicated in patients known to be hypersensitive to naloxone hydrochloride or to any of the other ingredients.

Seek emergency medical assistance immediately after initial use, keeping the patient under continued surveillance.

Risk of Recurrent Respiratory and CNS Depression: Due to the duration of action of naloxone relative to the opioid, keep the patient under continued surveillance and administer repeat doses of naloxone using a new nasal spray with each dose, as necessary, while awaiting emergency medical assistance.

Risk of Limited Efficacy with Partial Agonists or Mixed Agonists/Antagonists: Reversal of respiratory depression caused by partial agonists or mixed agonists/antagonists, such as buprenorphine and pentazocine, may be incomplete. Larger or repeat doses may be required.

Precipitation of Severe Opioid Withdrawal: Use in patients who are opioid dependent may precipitate opioid withdrawal characterized by body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, and tachycardia. In some patients, there may be aggressive behavior upon abrupt reversal of an opioid overdose. Monitor for the development of opioid withdrawal.

In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated and may also include convulsions, excessive crying, and hyperactive reflexes.

Abrupt Postoperative Reversal of Opioid Depression: Abrupt postoperative reversal of opioid depression may result in nausea, vomiting, sweating, tremulousness, tachycardia, hypotension, hypertension, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest. Serious sequelae of these events, including coma and death, have been reported. These events have primarily occurred in patients who had pre-existing cardiovascular (CV) disorders or received other drugs that may have similar adverse CV effects. Monitor these patients closely in an appropriate healthcare setting after use of naloxone HCl.

Adverse Reactions: The following adverse reactions were observed in a Naloxone HCl Nasal Spray clinical study: increased blood pressure, constipation, toothache, muscle spasms, musculoskeletal pain, headache, nasal dryness, nasal edema, nasal congestion, nasal inflammation, rhinalgia, and xeroderma.

Please see full Prescribing Information (https://sandoz-naloxone.com/pdf/naloxone-pi.pdf) **for additional safety information.**

Disclaimer

This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as “potential,” “can,” “will,” “plan,” “may,” “could,” “would,” “expect,” “anticipate,” “look forward,” “believe,” “committed,” “investigational,” “pipeline,” “launch,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this press release, or regarding potential future revenues from such products. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that the investigational or approved products described in this press release will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Neither can there be any guarantee that, if approved, such generic or biosimilar products will be approved for all indications included in the reference product’s label. Nor can there be any guarantee that such products will be commercially successful in the future. In particular, our expectations regarding such products could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; the particular prescribing preferences of physicians and patients; competition in general, including potential approval of additional generic or biosimilar versions of such products; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; litigation outcomes, including intellectual property disputes or other legal efforts to prevent or limit Sandoz from selling its products; general political, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases such as COVID-19; safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

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Sandoz, a Novartis division, is a global leader in generic pharmaceuticals and biosimilars. Our purpose is to pioneer access for patients by developing and commercializing novel,

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Appendix I-7

State Naloxone Access Rules and Resources

Read your state's access rules and find valuable resources about naloxone.

In states that adopt a naloxone access law, there is a 9-11% decrease in the number of opioid-related deaths, according to the National Bureau of Economic Research.

VIEW STATES

(A – G) (H – M) (N – R) (S – W)

* 3rd party prescribing allows a prescriber to write a prescription for a medication to someone other than the intended user of the medication.

* A standing order is a mechanism by which a healthcare provider with prescribing privileges, including a state health officer, writes a prescription that covers a large group of people.

State: Alabama
3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Statewide standing order from State Health Officer allows pharmacists to dispense naloxone at any pharmacy to family member, friend, or other individual, including law enforcement, in a postition to assist.

Other Resources: https://www.alabamapublichealth.gov/pharmacy/naloxone-dispensing.html

State: Alaska

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Law allows licensed healthcare providers (including pharmacists) to make naloxone available to anyone at risk or in a position to assist, directly, or via standing order.

Other Resources: http://dhss.alaska.gov/dph/director/pages/heroin-opioids/narcan.aspx

State: Arizona

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Statewide standing order from State Health Officer allows pharmacists to dispense naloxone to anyone without a prescription.

Other Resources:

https://azdhs.gov/documents/prevention/womens-childrens-health/injury-prevention/opioid-prevention/opioid-naloxone-faq.pdf

State: Arkansas

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Law allows licensed healthcare providers (including pharmacists) to make naloxone available to anyone at risk or in a position to assist someone at risk.

Other Resources:

https://www.pharmacyboard.arkansas.gov/Websites/pharmacy/images/home-page/Naloxone%20Protocol%202018%20Dec%206.pdf

State: California

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Law allows licensed healthcare providers (including pharmacists) to make naloxone available to anyone. Statewide standing order permits community organizations to dispense naloxone to a person at risk or in a position to assist a person at risk without a prescription.

Other Resources: https://www.chcf.org/wp-content/uploads/2018/10/NaloxoneAccessCA2018.pdf

State: Colorado

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Law allows pharmacies, which have a standing order written by a medical professional with prescriptive authority, to dispense naloxone to someone at risk, in a position to assist someone at risk, a first responder or a harm reduction organization without a prescription.
Other Resources: http://stoptheclockcolorado.org/

State: Connecticut
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Law allows certified pharmacists to dispense naloxone to anyone without a prescription.
Other Resources: https://portal.ct.gov/DCP/Drug-Control-Division/Drug-Control/Naloxone-Pharmacies

State: Delaware
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Standing order allows authorized Community-Based training programs and pharmacies to train and dispense naloxone to anyone who has completed the training without a prescription.
Other Resources: https://www.helpisherede.com/Get-Help/Overdose-Response#naloxone-availability

State: Florida
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Law allows pharmacists to dispense naloxone to patients, caregivers and first responders without a prescription.
Other Resources:
http://www.leg.state.fl.us/statutes/index.cfm?App_mode=Display_Statute&Search_String=&URL=0300-0399/0381/Sections/0381.887.html
http://www.myflfamilies.com/service-programs/substance-abuse/samh/treatment/opioidSTRP

State: Georgia
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Statewide standing order allows licensed pharmacies to dispense naloxone to anyone in a position to help – training advised but not required.
Other Resources:
https://dph.georgia.gov/sites/dph.georgia.gov/files/ChronicDisease/Standing%20Order%20Naloxone%5B2%5D.pdf

State: Hawaii
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Law allows healthcare providers (including pharmacists) to make naloxone

available to anyone at risk or in a position to assist someone at risk, or to a harm reduction organization.
Other Resources: https://www.hhhrc.org/overdose

State: Idaho
3rd Party: Yes
Standing Order: NO
Pharmacy Access Notes: Law allows prescribers and pharmacists to prescribe and dispense to anyone at risk, in a position to assist (including in course of official duties), or in the opinion of the pharmacist has a valid reason to possess. Effective July 1, 2019 – any licensed healthcare professional (ex: nurses) can dispense to anyone with a valid reason to possess naloxone.
Other Resources: No statewide distribution resource.
https://legislature.idaho.gov/wp-content/uploads/sessioninfo/2019/legislation/H0012.pdf

State: Illinois
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Statewide standing order from State Health Officer allows pharmacists and overdose education and naloxone distribution programs to dispense naloxone to anyone who requests it.
Other Resources: https://optin.in.gov/

State: Indiana
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Statewide standing order from State Health Officer allows pharmacists, and entities registered with the Indiana State Health Department to dispense naloxone to anyone who requests it.
Other Resources: https://www.in.gov/isdh/27387.htm

State: Iowa
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Statewide standing order form State Health Officer allows *trained* pharmacists to dispense naloxone to a person at risk, someone in a position to assist or to a first responder employed by law enforcement or fire department, wihtout a prescription.
Other Resources: https://pharmacy.iowa.gov/naloxone-standing-order

State: Kansas
3rd Party: NO
Standing Order: Yes
Pharmacy Access Notes: Statewide standing order/protocol allows pharmacist to dispense naloxone to anyone at risk, in a position to assist, a first responder or a school nurse without a prescription.
Other Resources: https://odcp.ky.gov/Stop-Overdoses/Pages/default.aspx
https://pharmacy.ky.gov/Documents/Sample%20Naloxone%20Protocol%20and%20Education%20Sheets.pdf

State: Kentucky
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Law allows pharmacists with a physician approved protocol to dispense naloxone to anyone without a prescription.
Other Resources: https://odcp.ky.gov/Stop-Overdoses/Pages/default.aspx
https://pharmacy.ky.gov/Documents/Sample%20Naloxone%20Protocol%20and%20Education%20Sheets.pdf

State: Louisiana
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Statewide standing order from State Health Officer allows a pharmacist to dispense to anyone (after required training), without a prescription.
Other Resources:
http://www.lsbme.la.gov/content/la-health-alert-information-2019-renewed-standing-order-naloxone
http://ldh.la.gov/index.cfm/page/2973

State: Maine
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Law allows a pharmacist with a standing order from a physician to prescribe to anyone at risk or in a position to help someone at risk without a prescription.
Other Resources: https://www.mainehealthequity.org/naloxone-training

State: Maryland
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Statewide standing order from State Health Officer allows pharmacists to dispense to anyone without a prescription.
Other Resources:
https://bha.health.maryland.gov/NALOXONE/Documents/FINAL%20Naloxone%20Stand.Order%20Ino%20one%20pager%

State: Massachusetts
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Statewide standing order from State Health Officer authorizes licensed pharmacists to dispense naloxone to anyone at risk or in a position to help someone at risk without a prescription.
Other Resources:
https://www.mass.gov/service-details/information-for-community-members-about-how-to-get-naloxone
https://www.mass.gov/service-details/overdose-prevention-training-resources

State: Michigan

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Law and statewide standing order from State Health Officer allow a trained pharmacist to dispense naloxone to anyone at risk or in a position to help someone at risk without a prescription.

Other Resources:

https://www.michigan.gov/mdhhs/0,5885,7-339-71550_2941_4871_79584_79585_79587_79591-409684--,00.html

State: Minnesota

3rd Party: NO

Standing Order: Yes

Pharmacy Access Notes: State law allows pharmacists, in collaboration with a registered practitioner, to provide naloxone to persons at risk for, or know of someone at risk for, opioid overdose.

Other Resources: https://www.health.state.mn.us/communities/opioids/mnresponse/naloxoneaccess.html

State: Mississippi

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Statewide standing order from State Health Officer allows pharmacists to dispense to anyone without a prescription.

Other Resources:

https://www.mbp.ms.gov/Documents/Naloxone_Standing_Order_Press_Release_5_31_2018.pdf

State: Missouri

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Statewide standing order from State Health Officer allows pharmacists to dispense to anyone at risk or in a position to help someone at risk without a prescription.

Other Resources: https://mohopeproject.org/resources/get-naloxone/

State: Montana

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Statewide standing order from State Health Officer allows pharmacists to dispense to anyone without a prescription.

Other Resources:

https://dphhs.mt.gov/Portals/85/publichealth/documents/EMSTS/Opioids/NaloxoneStandingOrder.pdf?ver=2017-10-06-131612-670

State: Nebraska

3rd Party: Yes

Standing Order: NO

Pharmacy Access Notes: Law and standing order allow pharmacists to dispense to anyone at risk or in a position to help someone at risk without a prescription.

Other Resources:

https://nebraskalegislature.gov/laws/statutes.php?statute=28-470

http://dhhs.ne.gov/publichealth/PDMP/Documents/Naloxone%20Standing%20Order%20-%20Expires%2008-10-19%20-%20Safranek.pdf

State: Nevada

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Law allows pharmacists in accordance with standardized procedures or under a standing order from a physician to dispense naloxone to patients, caregivers, person in a position to assit and first responders without a prescription.

Other Resources:

http://dpbh.nv.gov/uploadedFiles/dpbhnvgov/content/Resources/opioids/opioid_STR_Pamphlet_nasal_ap6.pdf

http://dpbh.nv.gov/uploadedFiles/dpbhnvgov/content/Resources/opioids/naloxone_toolkit_color.pdf

State: New Hampshire

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Law allows pharmacists with a standing order from a physician to dispense naloxone to patients, caregivers and first responders without a prescription.

Other Resources: http://anyoneanytime.wpengine.com/about/what-is-naloxone/

State: New Jersey

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Law allows any individual pharmacist or chain pharmacy with a standing order from the Department of Health to dispense naloxone to anyone without a prescription.

Other Resources:

https://nj.gov/health/integratedhealth/services-treatment/naloxone.shtml

State: New Mexico

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Law and statewide standing order from State Health Officer allow a pharmacist to dispense naloxone to anyone at risk or in a position to help someone at risk without a prescription.

Other Resources: https://nmhealth.org/about/phd/idb/hrp/

State: New York
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Law and standing orders allow pharmacists to dispense naloxone to anyone without a prescription.
Other Resources:
https://www.health.ny.gov/diseases/aids/general/opioid_overdose_prevention/

State: North Carolina
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Statewide standing order from State Health Officer allows pharmacists to dispense to anyone without a prescription.
Other Resources: http://www.naloxonesaves.org/

State: North Dakota
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Law allows a pharmacist to dispense directly or under a standing order to anyone at risk or in a position to assist someone at risk without a prescription.
Other Resources: https://prevention.nd.gov/stopoverdose/naloxone

State: Ohio
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Law allows a pharmacist under a standing order from a physician to dispense to anyone without a prescription.
Other Resources:
https://odh.ohio.gov/wps/portal/gov/odh/know-our-programs/violence-injury-prevention-program/projectdawn/

State: Oklahoma
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Law and standing orders allow participating pharmacies to dispense to anyone without a prescritpion, or through free state training program.
Other Resources: http://okimready.org/overdose/
http://www.thinksmartok.org/restoring-life

State: Oregon
3rd Party: Yes
Standing Order: NO

Pharmacy Access Notes: Law allows a pharmacist to dispense to anyone without a prescription.

Other Resources:

https://staysafeoregon.com/prevent-overdose/save-life-using-naloxone/

State: Pennsylvania

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Law allows a pharmacist under a standing order from a physician to dispense to anyone without a prescription.

Other Resources: https://www.ddap.pa.gov/overdose/Pages/Naloxone_Reversal.aspx

State: Rhode Island

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Pharmacists operating under a collaborative practice agreement (standing order from a physician) can dispense naloxone to anyone without a prescription.

Other Resources: https://preventoverdoseri.org/get-naloxone/

State: South Carolina

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Law allows any licensed pharmacist to dispense to anyone without a prescription.

Other Resources: http://naloxonesavessc.org/

State: South Dakota

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Law allows pharmacists to dispense, under a collaborative practice (protocol or standing order) with a physician, to anyone at risk or in a position to assist someone at risk without prescription.

Other Resources:

https://doh.sd.gov/documents/EMS/EMSNaloxone.pdf

State: Tennessee

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Law allows a pharmacist under a standing order from a physician to dispense to anyone at risk or in a position to assist someone at risk without a prescription.

Other Resources:

https://www.tn.gov/health/health-program-areas/health-professional-boards/csmd-board/csmd-board/naloxone-training-information.html

State: Texas
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Law and standing order allows accredited pharmacists to dispense to anyone at risk or in a position to assist someone at risk without a prescription.
Other Resources: http://sites.utexas.edu/naloxone/training/

State: Utah
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Law and standing order allow pharmacists to dispense to anyone at risk or in a position to help someone at risk without a prescription.
Other Resources:
http://www.utahnaloxone.org/utah-pharmacies-with-naloxone-rescue-kits/

State: Vermont
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Statewide standing order from State Health Officer allows pharmacists to dispense to anyone without a prescription.
Other Resources: http://www.healthvermont.gov/response/alcohol-drugs/narcan-naloxone-overdose-rescue

State: Virginia
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Law and standing order allow pharmacists and community organizations to dispense to anyone without a prescription.
Other Resources:
http://dbhds.virginia.gov/behavioral-health/substance-abuse-services/revive

State: Washington
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Law allows pharmacists and non-medical personnel to dispense under a Collaborative Drug Therapy Standing order from a legal prescriber to anyone without a prescription.
Other Resources:
http://depts.washington.edu/pcapuw/inhouse/FAQs_Naloxone_for_Community_Agencies.pdf

State: West Virginia
3rd Party: Yes
Standing Order: Yes
Pharmacy Access Notes: Law and statewide standing order from State Health Officer allow pharmacists to

dispense to anyone at risk or in a position to help someone at risk without a prescription.

Other Resources:

https://dhhr.wv.gov/bph/Documents/Standing%20Order%20for%20Naloxone%202018/Naloxone%20Prescription%20for%%2006.05.2018.pdf

State: Wisconsin

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Law and statewide standing order from State Health Officer allow participating pharmacies to dispense to anyone at risk or in a position to help someone at risk without a prescription.

Other Resources:

https://www.dhs.wisconsin.gov/opioids/standing-order.htm

State: Wyoming

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Law allows pharmacists to prescribe naloxone directly to anyone at risk or in a position assist someone at risk.

Other Resources:

https://health.wyo.gov/publichealth/prevention/substanceabuseandsuicide/opioid-information-wyoming/opioid-overdose-response/

State: D.C.

3rd Party: Yes

Standing Order: Yes

Pharmacy Access Notes: Law allows trained community health organizations (with a standing order from a physician) or healthcare providers including trained pharmacists to dispense to anyone at risk or in a position to help someone at risk without a prescription.

Other Resources: https://code.dccouncil.us/dc/council/laws/21-186.html

Appendix I-8

DOI: 10.1111/1475-6773.13125

RESEARCH ARTICLE

HSR Health Services Research

Will converting naloxone to over-the-counter status increase pharmacy sales?

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Funding information
National Institute on Drug Abuse, Grant/Award Number: P30DA040500

Objective: To estimate the own-price elasticity of demand for naloxone, a prescription medication that can counter the effects of an opioid overdose, and predict the change in pharmacy sales following a conversion to over-the-counter status.

Data Sources/Study Setting: The primary data source was a nationwide prescription claims dataset for 2010-2017. The data cover 80 percent of US retail pharmacies and account for roughly 90 percent of prescriptions filled. Additional covariates were obtained from various secondary data sources.

Study Design: We estimated a longitudinal, simultaneous equation model of naloxone supply and demand. Our primary variables of interest were the quantity of naloxone sold, measured as total milligrams sold at pharmacies, and the out-of-pocket price paid per milligram, both measured per ZIP Code and quarter-year.

Data Collection/Extraction Methods: Primary data came directly from payers and processors of prescription drug claims.

Principal Findings: We found that, on average, a 1 percent increase in the out-of-pocket price paid for naloxone would result in a 0.27 percent decrease in pharmacy sales. We predict that the total quantity of naloxone sold in pharmacies would increase 15 percent to 179 percent following conversion to over-the-counter status.

Conclusions: Naloxone is own-price inelastic, and conversion to over-the-counter status is likely to lead to a substantial increase in total pharmacy sales.

KEYWORDS
change in demand, naloxone, opioid overdose, over-the-counter conversion

1 | INTRODUCTION

In 2016, approximately 2.1 million US persons, 12 years of age and older, had an opioid use disorder,[1] and over 42 000 US persons died from a drug overdose attributed to opioids.[2] More opioid overdose deaths could be prevented if bystanders had access to naloxone, a prescription opioid antagonist medication that can counter the effects of an opioid overdose.[3] Naloxone has many appealing features from a public health standpoint. It has no effect on individuals who do not have opioids in their system, and the primary risk for those who do have opioids in their system is opioid withdrawal symptoms, which can be severe, but not when weighed against the risk of death for someone who is overdosing.[4] Moreover, naloxone is non-narcotic, has no abuse potential, and

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can be administered in some forms (eg, intranasal) by the general public with little-to-no training. Initiatives are underway across the country to increase layperson access to naloxone. All 50 states and the District of Columbia have modified laws related to naloxone access; for example, 23 states currently have statewide standing orders for naloxone, which allow pharmacists to dispense naloxone on request, and an additional 24 states allow jurisdictions to pass naloxone standing order laws.[5] Major pharmacy corporations such as Walgreens and CVS have recently stated their commitment to stocking and selling naloxone; however, they must do so in accordance with the state's rules and regulations.[6,7] An alternative to standing orders that has received a great deal of support, including from the US Food and Drug Administration, is to change the prescribing status of naloxone from prescription-only to over-the-counter (OTC) status.[8-11]

Changing the prescribing status of naloxone to OTC is expected to further reduce access barriers, thereby resulting in an increase in demand and a concomitant increase in quantity demanded at any given price. However, if there is a loss of insurance coverage that accompanies the change to OTC status or manufacturers decide to increase prices for OTC products above prices for prescription products, out-of-pocket price increases would put downward pressure on the quantity of naloxone demanded. Which effect dominates (ie, the upward pressure on quantity demanded due to the increase in demand, or the downward pressure on quantity demanded due to the increase in out-of-pocket price) is an empirical question. Therefore, the initial objective of this study was to use nationwide, longitudinal, and comprehensive prescription claims data to estimate the demand and supply functions for naloxone purchased at US retail pharmacies. The price per unit for a given medication often varies by pharmacy, even within the same geographic location.[12] Our ability to observe variation in the out-of-pocket price paid for naloxone by consumers at retail pharmacies across the United States, and the quantities purchased at those prices, while controlling for potentially confounding factors, allowed us to characterize the naloxone demand curve for this market. We used a simultaneous equation model to account for the endogeneity resulting from the simultaneous influence that demand and supply functions have on one another. We then estimated the own-price elasticity of demand for naloxone purchased at pharmacies (ie, the percentage change in quantity demanded given a one percent increase in the out-of-pocket price), which allowed us to predict the change in total pharmacy naloxone sales following a conversion to OTC, based on different assumptions of changes in demand and price.

2 | STUDY DATA AND METHODS

2.1 | Analytic overview

The quantity exchanged of any good in a market is a function of both supply and demand; thus, econometric estimation of either the demand or supply function requires the consideration of the simultaneous influence that one has on the other.[13] To account for this, we estimated a simultaneous equation model. The unit of observation was the pharmacy ZIP Code per quarter-year. All values were adjusted to 2016 US dollars using the prescription drug consumer price index.[14]

There are currently three primary naloxone delivery systems (injection, auto-injection, and intranasal). Even though the auto-injection and intranasal systems are most likely to receive OTC status, we included all available formulations and delivery systems in our model. The reason for this is that the auto-injection and intranasal delivery systems have only been on the market since 2014 and 2015, respectively, and therefore, by themselves, would provide very little information upon which to estimate our model.

2.2 | Demand function

The demand equation for naloxone was modeled as a function of the out-of-pocket price paid by consumers at the pharmacy, consumer income, other consumer demographic and socioeconomic characteristics that may be associated with the quantity of naloxone they are willing and able to purchase at any given price, the severity of the opioid use disorder epidemic in the area, local pharmacy naloxone access regulations, and other regional characteristics. Binary variables representing the presence of the auto-injection (Evzio®, kaléo, Richmond, VA, USA) and intranasal (Narcan®, ADAPT Pharma, Radnor, PA, USA) delivery systems in the market were also included in the demand equation, since their introduction likely influenced the overall demand for naloxone.

2.3 | Price function

The US pharmaceutical manufacturing industry for specific therapeutic markets is more accurately characterized as an oligopoly than a perfectly competitive market.[15] As such, we estimated a price equation similar to that of Keeler et al,[16] which better reflects the supply side of an oligopolistic market. The naloxone price equation was modeled as a function of the cost of production, distribution, and selling; variations in the price elasticity of demand over time; and market competition. The binary variables indicating the availability of the auto-injection and intranasal naloxone delivery systems were also included to control for their potential effect on market competitiveness and the elasticity of demand.

2.4 | Identification

To control for the endogeneity in a two-equation system and ensure that the system is identified, each equation must contain at least one unique exogenous variable that is correlated with the endogenous right-hand-side variable, but not the residual, in the other equation. These “extra” exogenous variables serve as instruments for the endogenous right-hand-side variable. Consumer demographic and socioeconomic characteristics that are associated with their preferences for naloxone at any given price do not belong in the supply function from a theoretical standpoint, and therefore, those measures were excluded from the price equation. For the same reason, the

production cost and market competition measures were excluded from the demand equation. Therefore, our simultaneous system of equations was likely overidentified, indicating that unique estimates for all parameters could be calculated. As an additional test of overidentification, we estimated a reduced-form generalized method of moments equation and calculated Hansen's J statistic using Stata's overid command; the results indicated that the instruments are valid and the equation is overidentified.

2.5 | Data and measures

Our primary data source was a nationwide prescription claims database from Symphony Health.[17] The Symphony Health data contain information from over 80 percent of US retail pharmacies and account for roughly 90 percent of prescriptions filled in those locations. Our study focused solely on pharmacy sales to individual consumers, as opposed to facilities such as private and government hospitals, clinics, home health care providers, HMO captive pharmacies, mail-order pharmacies, and prisons. Symphony data come directly from payers and processors of prescription drug claims, and contain information on consumer out-of-pocket costs, as well as consumer demographic and socioeconomic factors. All payers are captured by the data, including commercial insurers, Medicare fee-for-service, Medicare Advantage, Medicaid, and self-pay. Additionally, pharmacies are required to resubmit files containing errors in more than 2 percent of required fields. Our study sample included all ZIP Code/quarter-year observations for which naloxone pharmacy sales had been recorded, and we had information on the total milligrams of naloxone sold and the associated out-of-pocket prices for the time frame of 2010-2017. In regions where ZIP Codes did not contain three or more unique pharmacies, pharmacy claims data were aggregated to the three-digit ZIP Code level by the data distributor, for purposes of confidentiality.

Quantity of naloxone demanded was measured as total milligrams (mg) sold per ZIP Code, per quarter-year. Out-of-pocket price paid for naloxone was measured as the out-of-pocket price paid per mg sold in a given ZIP Code, per quarter-year. We included the following customer demographic and socioeconomic information to control for heterogeneity in their preferences for naloxone at any given price, all of which were operationalized as means or percentages per ZIP Code, per quarter-year: age, race/ethnicity, gender, education, payer type, and annual income by quintile. The severity of the opioid use disorder epidemic in the area was measured using the reported opioid overdose death rate in the corresponding county during the prior year.[18] Two binary variables were created to indicate whether the state in which the ZIP Code resides had a statewide standing order in place at the time or allowed standing orders to be implemented by jurisdiction; ZIP Codes in states that did not have either regulation in place at a given time served as the reference case. Other local characteristics, such as the political environment around naloxone distribution and influence of community members' opinions, were controlled for using state fixed effects and Rural-Urban Commuting Area (RUCA) codes to identify the degree of rurality associated with each ZIP Code.[19] RUCA codes combine the Bureau of Census' "urbanized area" and "urban cluster" definitions with information on work commutes to create a more refined measure of community isolation.

The cost of naloxone production, distribution, and selling was controlled for using the average producer price index value for pharmaceutical preparation manufacturing overall, by quarter-year.[20] The number of naloxone manufacturers in the quarter-year was included in the price equation as a measure of market competitiveness. An exponential time trend was included in the price equation to reflect changes in the price elasticity of demand over time, as well as technological improvements that could have increased the efficiency with which manufacturers were able to produce naloxone. Finally, binary variables indicating the availability of the auto-injection and intranasal naloxone delivery systems were included in both the demand and price equations due to their potential effects on demand and supply.

2.6 | Analysis

A multivariable generalized structural equation model (GSEM) with clustered standard errors was used to estimate the demand and price functions for naloxone. The GSEM combines the capabilities of structural equation models (SEMs) and generalized linear models (GLMs). SEMs are flexible multiple equation regression models that allow for complex relationships between factors of interest, and as such, SEMs encompass simultaneous equation models. The GLM, and thus the GSEM, allows the most appropriate mean and variance functions to be chosen for each equation in the system, according to the fit of the data.[21] The modified Parks test was used as a guide to choosing the appropriate variance structure (ie, family), and the Pearson Correlation, Pregibon Link, and Modified Hosmer and Lemeshow tests were used to inform the decision of which mean (ie, link) function was most appropriate.[21]

The opioid overdose death rate was suppressed for regions with fewer than 10 reported overdose deaths.[18] Given that we know the reason for the missingness of observations in this variable and had observed variables that were strong predictors of the probability of the missingness (ie, the RUCA code and state fixed effects), we used inverse probability weighting within a GLM framework to predict and replace these missing values prior to the inclusion of the opioid overdose death rate in the GSEM.[22] The average missingness per quarter-year ranged from 19 percent to 41 percent, with a mean of 26 percent across all time periods.

2.6.1 | Prediction of change in quantity of naloxone sales

Our prediction of the change in the quantity of naloxone sold in pharmacies following a conversion to OTC was based on our estimated own-price elasticity of demand for naloxone, and estimates obtained from the literature regarding (a) the difference between the out-of-pocket price for medications covered by insurance and the price paid for those medications after a change in prescribing

status to OTC, (b) the own-price elasticity of demand for nicotine replacement therapies following their conversion to OTC, and (c) the estimated effect that the conversion to OTC had on the quantity of nicotine replacement therapies demanded. Nicotine replacement therapies were chosen because they are the only other substance use disorder pharmacotherapy to have experienced a change from prescription-only to OTC status in the United States, and the change to OTC status created an entirely new OTC market with potential public health benefits,[23] as would naloxone.

We defined eight scenarios that describe a range of predicted changes in naloxone sales following OTC conversion. We considered two levels of demand increase: 78 percent (based on the low estimate for nicotine patches) and 180 percent (based on the estimate for nicotine gum).[16] We also considered four out-of-pocket price increases based on ranges observed in Maryland for indemnity/managed care plan enrollees (2 percent and 113 percent) and Kaiser Permanente enrollees (54 percent and 233 percent), for four other OTC conversion products (cromolyn sodium—Nasalcrom®, tioconazole—Vagistat®, ketoconazole—Nizoral®, and terbinafine—Lamisil®).[24]

2.6.2 | Sensitivity analyses

We conducted one-way sensitivity analyses to find the threshold values for the percentage increase in price, percentage increase in quantity demanded, and own-price elasticity of demand that would result in no change in total naloxone sales following OTC. We also varied the "extra" exogenous variables that serve as instruments in the demand and price functions. Finally, we calculated the most likely average out-of-pocket price increase that occurred in the market for nicotine patches and gum. The estimated price increases of 26 percent (patches) and 33 percent (gum) were calculated based on the own-price elasticities of demand for these products following OTC conversion (−2.33 and −2.46, respectively),[25] and the observed unadjusted increase in total sales that occurred after OTC conversion (18 percent and 100 percent, respectively).[16]

2.6.3 | Strengths and limitations

A major strength of this paper is the longitudinal, nationwide, comprehensive pharmaceutical claims data, which included all payer types, out-of-pocket prices, and demographic and socioeconomic variables. Our generalized structural equation model, which allowed us to choose the most appropriate mean and variance functions according to our data and estimate a simultaneous system of supply and demand equations, is also a major strength.

The fact that our data failed to capture 20 percent of pharmacies is a limitation; however, according to the data distributor, pharmacies that are not included in the data are typically independent or associated with relatively small chains, and these pharmacies may be less likely to dispense naloxone.[26-29] The pharmacy ZIP Code serving as a proxy for a customer's geographic location is a limitation; however, since naloxone must be purchased in-person, even under a standing order, we believe this to be a reasonable assumption. The CDC's compressed mortality file was only available at the county level, and data were suppressed for regions with fewer than 10 overdose deaths; however, these observations were accounted for using a proven technique to address missing-data bias.[22] We were unable to determine whether ZIP Codes in states that allowed local standing orders actually had one in place. Similarly, for ZIP Codes in states with statewide standing orders we were unable to determine whether pharmacies were actually adhering to the standing order. We were unable to measure the production, distribution, and selling costs for naloxone specifically, but were able to include the producer price index for pharmaceutical preparation manufacturing as a proxy. We do not have sufficient data to forecast the impact that a conversion of naloxone to OTC would have on opioid overdose education and naloxone distribution by harm reduction agencies, for example, information on the likelihood that persons who are unable or unwilling to purchase naloxone at a higher out-of-pocket price would obtain it by other means.

3 | RESULTS

Descriptive statistics by ZIP Code/quarter-year over the observation period are presented in Table 1. The mean number of milligrams of naloxone sold for a ZIP Code/quarter-year where naloxone pharmacy sales had been recorded was 165, at an average out-of-pocket price of $28.11/mg (SE = $2.20/mg). On average, 34 percent of ZIP Code/quarter-year observations were in a state with a statewide standing order and 48 percent were in a state that allowed local standing orders. The average age of naloxone consumers was 51 years, and the plurality of those for whom we had complete demographic and socioeconomic information was white, female, had a high school diploma or GED, and was making under $30 000 per year. Over 40 percent of naloxone prescriptions were purchased using Medicare or Medicare Advantage. Almost 79 percent of ZIP Code/quarter-year observations that contained a recorded naloxone pharmacy sale were associated with a metropolitan area, and the mean opioid overdose death rate in the associated counties in the prior year was 9.71/100 000 persons. The national opioid overdose death rate over this period ranged from just under 7/100 000 to over 13/100 000 persons.

3.1 | Demand function

The results from the estimated demand function are presented in Table 2. The coefficient estimate for the log of the out-of-pocket price per mg of naloxone is −0.27 (95% CI: −0.32, −0.22; $P < 0.01$), indicating that a 1 percent increase in the out-of-pocket price would result in a 0.27 percent decrease in the quantity of naloxone demanded from pharmacies. Having a statewide standing order in place or having a law allowing standing orders were both associated with a significant increase in naloxone demanded from pharmacies (1.36 percent and 0.80 percent, respectively; $P < 0.01$), relative to ZIP Codes in states without such regulations. ZIP Codes located

TABLE 1 Descriptive statistics for naloxone pharmacy claims by ZIP Code/Quarter-Year, 2010-2017

n = 10 468	Mean	SE
Naloxone characteristics		
Average total milligrams of naloxone	165.00	5.78
Average price per milligram of naloxone	$28.11	$2.20
Demographic characteristics of naloxone consumers		
Average age	50.76	0.12
Race/ethnicity		
% White	49.64	0.36
% Black	8.13	0.20
% Hispanic	4.02	0.14
% Other ethnicity	1.11	0.07
% Unknown ethnicity	37.11	0.35
Sex		
% Male	46.28	0.35
% Female	53.72	0.35
Socioeconomic characteristics of naloxone consumers		
Education		
% College degree	27.01	0.25
% Associate's degree	13.31	0.31
% High school diploma or GED	23.65	0.31
% Unknown education	36.03	0.34
Income		
% Under 30k	18.31	0.27
% 30k-49k	10.82	0.21
% 49k-79k	10.89	0.21
% 79k-99k	8.58	0.19
% 100 + k	13.76	0.25
% Unknown income	37.63	0.35
Payer		
% Commercial	37.35	0.35
% Assistance programs	3.80	0.14
% Cash	8.80	0.22
% Managed Medicare	9.63	0.23
% Medicaid	7.61	0.19
% Medicare	32.80	0.34
ZIP Code characteristics		
% ZIP Code/quarter-year with statewide standing order	33.91	0.46
% ZIP Code/quarter-year with nonstatewide standing order law	47.66	0.49
ZIP Code size		
% Micro[a]	9.13	0.28
% Small[b]	12.20	0.32
% Metro[c]	78.67	0.40
County opioid overdose death rate (per 100k persons) in preceding year	9.71	0.06

[a]RUCA[19] codes 4 (primary flow within a "large urban cluster" = 10 000-49 999 persons) through 6 (primary flow 10%-30% to a "large urban cluster").
[b]RUCA codes 7 (primary flow within a "small urban cluster" = 2500-9999 persons) through 10 (rural = primary flow outside an urban cluster or area).
[c]RUCA codes 1 (primary flow within an "urbanized area" >9999) through 3 (primary flow 10%-30% to an "urbanized area").

in counties with relatively high opioid overdose death rates in the preceding year sold more naloxone at pharmacies; specifically, every one point increase in the opioid overdose death rate was associated with a 0.04 percent increase in pharmacy naloxone sales in the subsequent year ($P < 0.01$). The introduction of the naloxone nasal spray (Narcan®) was associated with a 2 percent increase in naloxone pharmacy sales, while the effect of the introduction of the naloxone auto-injector (Evzio®) was nonsignificant. Demographic and socioeconomic factors associated with higher pharmacy sales of naloxone included increased age; residing in a metropolitan area; having a 4-year college degree, vs a high school diploma or GED; identifying as white/Caucasian, vs Hispanic; and having insurance coverage provided by Medicare, Medicare Advantage, or Medicaid, relative to commercial insurance.

3.2 | Price function

The results from the price function are also displayed in Table 2. The number of naloxone manufacturers was negatively associated with the out-of-pocket pharmacy price; specifically, each additional naloxone manufacturer resulted in a 0.69 percent (95% CI: −0.98, −0.39; $P < 0.01$) decrease in the out-of-pocket price. The producer price index for pharmaceutical preparation manufacturing was also negatively associated with the out-of-pocket price, although the effect was small ($B = -0.03$, $P = 0.01$). According to Rosenberg et al,[30] the raw material costs for naloxone were fairly stable over this time period, but unfortunately, we do not know how other costs of naloxone manufacturing, distribution, and selling were changing. The introductions of the naloxone nasal spray (Narcan®) and auto-injector (Evzio®) were associated with significant increases in the out-of-pocket pharmacy price for naloxone (2.46 percent and 1.69 percent, respectively; $P < 0.01$).

3.3 | Prediction of change in quantity demanded

Applying the own-price elasticity of demand for naloxone (−0.27) to the observed out-of-pocket price increases associated with OTC product conversions in Maryland (2 percent to 233 percent),[24] and the estimated demand increases for nicotine patches and gum (78 percent and 180 percent, respectively),[16] we predict an increase in naloxone sales of 15 percent to 77 percent using the estimated demand increase for nicotine patches, and 117 to 179 percent

TABLE 2 GSEM demand and supply function results

	Coef.	Std. Err.	$P > \|z\|$
Demand function			
Naloxone characteristics			
Log out-of-pocket price per mg	−0.27	0.02	<0.01
Auto-injector on market	0.19	0.13	0.15
Nasal spray on market	1.99	0.10	<0.01
Demographic characteristics			
Average age	0.01	0.00	<0.01
Race/ethnicity			
White	Reference		
Black	0.10	0.21	0.63
Hispanic	−0.59	0.22	0.01
Other ethnicity	0.36	0.49	0.47
Unknown ethnicity	0.06	0.41	0.88
Sex			
Male	Reference		
Female	−0.06	0.09	0.49
Opioid overdose death rate in preceding year	0.04	0.01	<0.01
Socioeconomic characteristics			
Education			
College degree	Reference		
Associate's degree	−0.26	0.20	0.21
High school diploma or GED	−0.47	0.14	<0.01
Unknown education	−0.30	0.54	0.58
Income			
Under 30k	0.33	0.17	0.06
30k-49k	0.16	0.17	0.36
49k-79k	Reference		
79k-99k	0.24	0.19	0.20
100 + k	0.13	0.18	0.46
Unknown income	0.24	0.36	0.50
Payer			
Commercial	Reference		
Assistance programs	0.44	0.29	0.12
Cash	0.10	0.12	0.43
Medicaid	0.54	0.22	0.01
Medicare	0.24	0.12	0.05
Managed Medicare	1.00	0.30	<0.01
ZIP Code characteristics			
Statewide standing order present	1.36	0.12	<0.01
Jurisdictional standing order law present	0.80	0.10	<0.01
ZIP Code size			
Micro	−0.96	0.12	<0.01
Small	−0.81	0.12	<0.01
Metro	Reference		
Constant	0.60	0.31	0.06
Price function			
Producer price index	−0.03	0.01	0.01
Manufacturers on market	−0.69	0.15	<0.01
Time trend	0.00	0.00	0.41
Auto-injector on market	2.46	0.36	<0.01
Nasal spray on market	1.69	0.42	<0.01
Constant	5.71	13.02	0.66

Notes: Dependent variables are log of total milligrams of naloxone sold (demand function) and log of out-of-pocket price per mg of naloxone sold (supply function). State fixed effects (not shown) were included in the demand function equation.

using the estimate for nicotine gum (Table 3, Figure 1). Predicted sales increases are substantially lower for nicotine patches and gum, due to their substantially higher estimated own-price elasticities of demand. Based on the scenario that produced the lowest predicted naloxone sales increase (15 percent), we find that a 288 percent price increase (vs 233 percent), a 63 percent demand increase (vs 78 percent), or an own-price elasticity of −0.34 (vs −0.27 percent) would result in no change in total naloxone pharmacy sales. Applying the estimated out-of-pocket price increases following OTC conversion for nicotine patches (26 percent) and nicotine gum (33 percent), our estimated own-price elasticity of demand for naloxone, and the relevant estimated effects of OTC conversions on demand for nicotine patches and gum, we predict a 71 to 171 percent increase in total naloxone pharmacy sales.

4 | DISCUSSION

Our primary outcome of interest was the own-price elasticity of demand for naloxone pharmacy sales. We found that the demand for naloxone was inelastic with regard to changes in its out-of-pocket price during our observed time period, with an elasticity of −0.27, which indicates that a 1 percent increase in the out-of-pocket price for naloxone would only result in a 0.27 percent decrease in the quantity of naloxone sold in pharmacies. This figure is much smaller in magnitude than the estimated own-price elasticity of the nicotine gum and patch replacement therapies immediately following their conversion to OTC, −2.46 and −2.33, respectively,[25] but slightly larger than recent own-price elasticity of demand estimates of prescription medications for the period 2005-2009, which ranged from −0.02 for NSAIDs/opioids to −0.16 for smoking cessation medications.[31] The relatively large own-price elasticities of demand for the

OTC nicotine replacement therapies may be the result of the marginal consumer being less committed to smoking cessation, and thus more responsive to price changes, than those who seek the prescription products. Similarly, the marginal OTC consumer may feel there are more substitutes for the OTC products, including those that are prescription-only, whereas prescription-only consumers may have already tried the OTC products, with limited success.

Applying the estimated own-price elasticity of demand for naloxone to estimates from the literature regarding changes in price and demand around OTC conversion, we predict that naloxone pharmacy sales would increase between 15 percent and 179 percent if naloxone was moved to OTC. After estimating the mean percentage price increase in nicotine replacement therapies that occurred at the point of purchase following OTC, we narrowed our prediction of the change in naloxone sales following OTC to a 71 percent to 171 percent increase.

In sensitivity analyses we estimated that even at a price increase of 233 percent for naloxone, the increase in demand associated with OTC would have to fall below 68 percent, or the absolute value of the own-price elasticity of demand would have to increase to −0.34, before total pharmacy sales would decline. The own-price elasticity

TABLE 3 Predicted changes in naloxone sales following conversion to OTC

Price increase[a]	2%	54%	113%	233%
Nicotine gum assumptions				
Demand increase[b]	180%	180%	180%	180%
OOP elasticity of demand	−0.27	−0.27	−0.27	−0.27
Change in quantity due solely to price increase	−0.54%	−14.58%	−30.51%	−62.91%
Change in total sales after accounting for all supply and demand side effects	179%	165%	149%	117%
Nicotine patch assumptions				
Demand increase[b]	78%	78%	78%	78%
OOP elasticity of demand	−0.27	−0.27	−0.27	−0.27
Change in quantity due solely to price increase	−0.54%	−14.58%	−30.51%	−62.91%
Change in total sales after accounting for all supply and demand side effects	77%	63%	47%	15%

OOP, out of pocket; OTC, over the counter.
[a]See Gianfrancesco et al.[24]
[b]See Keeler et al.[16]

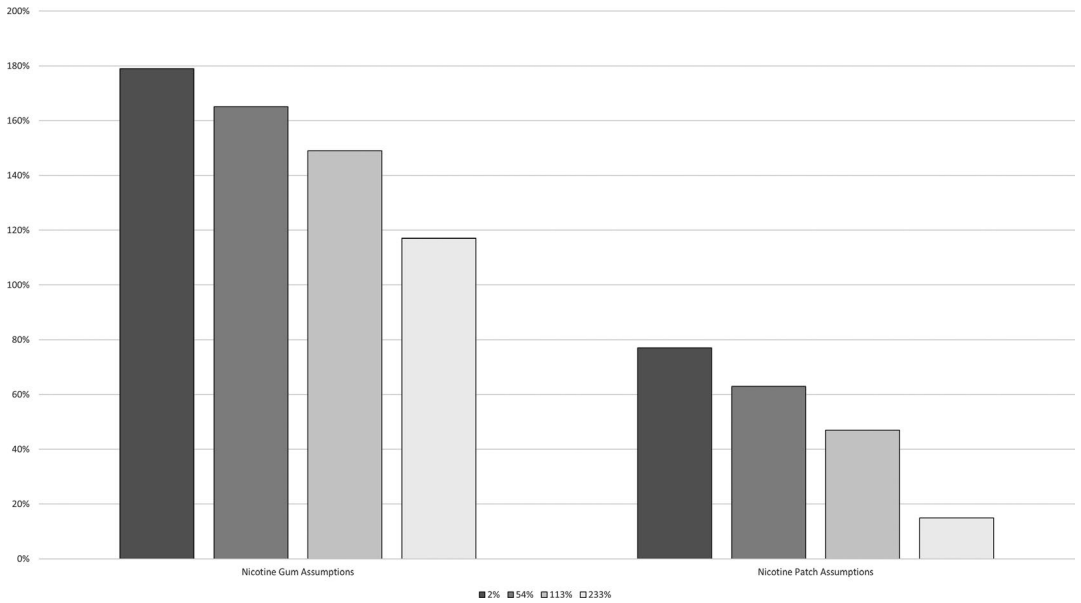

FIGURE 1 Predicted changes in naloxone sales following conversion to OTC
Source: Authors' analysis of the 2010-2017 Symphony Health pharmacy claims database.

of demand was robust to varying the instruments in the demand and price functions. Moreover, theoretically, we would not expect the elasticity of demand for naloxone to change much following a move to OTC given that it is a life-saving drug for which there are no substitutes, and, at a current retail price of $150 ($18.75/mg) for two intranasal devices,[32] we do not expect it to become a significantly larger proportion of the average consumer's budget, even if most insurers choose not to cover the drug. Of course, the larger the increase in demand, the more robust the findings are to increases in price and elasticity of demand. We posit that a relatively large increase in naloxone demand is reasonable given the significant increase associated with state laws that allow local naloxone standing orders, the even larger effect associated with statewide standing orders, and the continued calls to increase naloxone among the general public, including from the US Surgeon General[33]; especially when considered in the context of the recent New York Times investigation, which found that of the 720 pharmacies in New York City that were on the city's list of pharmacies who sell naloxone under the state's standing order, only 38 percent had it in stock and were willing to dispense it without a prescription.[34] Additionally, moving naloxone to OTC would help normalize the purchasing process, and likely reduce concerns of stigma by customers, which would also serve to increase demand.[35] Finally, the potential to obtain FDA approval to sell naloxone OTC would likely draw additional manufacturers into the marketplace, similar to the nicotine replacement therapy market following OTC conversion,[23] which in turn would put downward pressure on price.

The degree to which a conversion of naloxone to OTC would affect public health will depend on how the change affects those persons who would be most likely to observe an overdose and use the product. That is, will the number of opioid overdose reversals among new purchasers of naloxone be greater than the number forgone by current purchasers who would be unwilling or unable to purchase naloxone at a higher out-of-pocket price? An additional consideration is the manner in which these two groups of potential consumers differ. For example, if insurers for low-income individuals, who may be more sensitive to price increases, turn out to be less likely to continue coverage of naloxone after OTC conversion, this could lead to large out-of-pocket price increases for this population,[24] in which case public health could actually be adversely affected and economic disparities could increase.

5 | CONCLUSION

Converting naloxone from prescription-only to over-the-counter status is likely to lead to a substantial increase in total pharmacy sales. All else constant, as the prevalence of naloxone increases among the general public, so too should the opportunities to reverse opioid overdoses, thereby giving overdose survivors another chance to initiate treatment. However, the public health impact will depend on how likely the new population of OTC naloxone consumers are to encounter an overdose and use the product relative to the population of existing naloxone consumers.

ACKNOWLEDGMENTS

Joint Acknowledgment/Disclosure Statement: All authors are funded by the National Institute on Drug Abuse (Grant No. P30DA040500). Dr. Murphy has consulted for Sandoz Inc. on an unrelated project. The authors wish to thank David Powell, PhD, for assistance with the study design. The authors report no other disclosures.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Murphy SM, Morgan JR, Jeng PJ, Schackman BR. Will converting naloxone to over-the-counter status increase pharmacy sales? *Health Serv Res*. 2019;54:764–772. https://doi.org/10.1111/1475-6773.13125

Appendix I-9

JAMA Network Open

Original Investigation | Health Policy

Availability and Cost of Naloxone Nasal Spray at Pharmacies in Philadelphia, Pennsylvania, 2017

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Abstract

IMPORTANCE Despite the increasingly important role of pharmacies in the implementation of naloxone access laws, there is limited information on the impact of such laws at the local level.

OBJECTIVE To evaluate the availability (with or without a prescription) and cost of naloxone nasal spray at pharmacies in Philadelphia, Pennsylvania, following a statewide standing order enacted in Pennsylvania in August 2015 to allow pharmacies to dispense naloxone without a prescription.

DESIGN, SETTING, AND PARTICIPANTS A survey study was conducted by telephone of all pharmacies in Philadelphia between February and August 2017. Pharmacies were geocoded and linked with the American Community Survey (2011-2015) to obtain information on the demographic characteristics of census tracts and the Medical Examiner's Office of the Philadelphia Department of Public Health to derive information on the number of opioid overdose deaths per 100 000 people for each planning district. Data were analyzed from March 2018 to February 2019.

MAIN OUTCOMES AND MEASURES Availability and out-of-pocket cost of naloxone nasal spray (with or without a prescription) at Philadelphia pharmacies overall and by pharmacy and neighborhood characteristics.

RESULTS Of 454 eligible pharmacies, 418 were surveyed (92.1% response rate). One in 3 pharmacies (34.2%) had naloxone nasal spray in stock; of these, 61.5% indicated it was available without a prescription. There were significant differences in the availability of naloxone by pharmacy type and neighborhood characteristics. Naloxone was both more likely to be in stock (45.9% vs 27.8%; difference, 18.0%; 95% CI, 8.3%-27.8%; $P < .001$) and available without a prescription (80.6% vs 42.2%; difference, 38.4%; 95% CI, 23.0%-53.8%; $P < .001$) in chain stores than in independent stores. Naloxone was also less likely to be available in planning districts with very elevated rates of opioid overdose death (≥50 per 100 000 people) compared with those with lower rates (31.1% vs 38.5%). The median (interquartile range) out-of-pocket cost among pharmacies offering naloxone without a prescription was $145 ($119-$150); costs were greatest in independent pharmacies and planning districts with elevated rates of opioid overdose death.

CONCLUSIONS AND RELEVANCE Despite the implementation of a statewide standing order in Pennsylvania more than 3 years prior to this study, only one-third of Philadelphia pharmacies carried naloxone nasal spray and many also required a physician's prescription. Efforts to strengthen the implementation of naloxone access laws and better ensure naloxone supply at local pharmacies are warranted, especially in localities with the highest rates of overdose death.

JAMA Network Open. 2019;2(6):e195388. doi:10.1001/jamanetworkopen.2019.5388

Key Points

Question What is the availability of naloxone at pharmacies in Philadelphia, Pennsylvania, 3 years after the implementation of a statewide standing order in Pennsylvania allowing pharmacists to dispense naloxone without a prescription?

Findings This survey study of 418 pharmacies in Philadelphia found that only one-third carried naloxone nasal spray and many also required a physician's prescription, including pharmacies in communities with the highest rates of opioid overdose death.

Meaning Efforts to strengthen the implementation of naloxone access laws and better ensure naloxone supply at local pharmacies are warranted, especially in localities with high rates of opioid overdose death.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

One of many important strategies to address the opioid epidemic is to increase the distribution of naloxone, a safe and effective reversal agent for opioid overdoses. Within the past 2 decades, every state in the United States has passed a naloxone access law to increase the availability of this life-saving opioid antidote, including a nasal spray form, to laypersons.[1] However, several reports have documented slow implementation of naloxone access laws in states without a statewide standing order.[2,3] Pennsylvania, a state with high opioid mortality, was one of the first states to implement a statewide standing order in August 2015, allowing pharmacists to dispense naloxone without a physician's prescription to any layperson.[4] Findings from a study conducted between December 2016 and April 2017 in Pennsylvania indicate pharmacist awareness of the statewide standing order for naloxone, however, is lacking, particularly in independent pharmacies.[5]

Despite the increasingly important role of pharmacies in the implementation of naloxone access laws, there is limited information on the impact of such laws, including statewide standing orders, at the local level. We conducted a telephone survey of all pharmacies in Philadelphia, Pennsylvania, between February and August 2017 to examine the availability and out-of-pocket cost of naloxone nasal spray. We were interested in the availability both with and without a prescription from a licensed prescriber, and we examined the association between availability and pharmacy and neighborhood characteristics in Philadelphia. We hypothesized that naloxone was more likely to be available in neighborhoods with elevated rates of opioid overdose death (OOD) and that independent pharmacies would be less likely than retail chains to offer it.

Methods

Study Design and Data Source

This study followed the American Association for Public Opinion Research (AAPOR) reporting guideline. A list of all licensed retail pharmacies was obtained from the National Council for Prescription Drug Programs.[6] In February 2017, we used this list to identify currently active pharmacies and their contact information (via Google searches). We attempted to reach all active pharmacies on this list or a 100% sample of our sampling frame. Criteria for ineligibility included duplicate listing, nonretail (eg, clinic-based) pharmacy or closed-door facility, or pharmacy was permanently closed when we attempted to contact them during our study period. According to the AAPOR guidelines for telephone surveys,[7] the sampling frame and the eligibility criteria were determined a priori; we provide a flowchart detailing the number pharmacies that were ineligible or did not respond (eFigure in the Supplement). Of 454 eligible pharmacies, 418 participated in our survey (92.1% response rate, using AAPOR response rate 1[7]). We used the American Community Survey (2011-2015) to obtain information about the demographic characteristics of neighborhoods at census tract level and the Medical Examiner's Office of the Philadelphia Department of Public Health to derive information on the number of OODs per 100 000 people for each planning district.[8,9] This study was not considered human subjects research by the University of Illinois at Chicago institutional review board.

Outcomes

Our primary outcome was availability of naloxone nasal spray (hereafter referred to as *naloxone*) with or without an individual prescription. To assess the availability of naloxone, a trained interviewer posing as a customer asked to speak to the pharmacist and asked, "Is naloxone nasal spray or Narcan available or in stock at your pharmacy right now?" If it was not in stock, the interviewer asked whether it could be ordered. If naloxone was in stock, the interviewer then inquired about prescription requirements by asking "Can I get it from your pharmacy without a prescription from my doctor?" If the pharmacy responded affirmatively, the interviewer then inquired about age requirements and the price without insurance (if a range was provided, the lowest price was used).

Pharmacy and Neighborhood Characteristics

We categorized pharmacies as chains, independents, food stores, or mass retailers based on the National Council for Prescription Drug Programs classification for pharmacy type.[6] We defined low-income neighborhoods as census tracts in which at least 20% of the population had a household income at or below the federal poverty level or in which the median household income did not exceed 80% of Philadelphia's median household income ($37 479). We created tertiles for the percentage of population that self-identified as minority (nonwhite). We also derived information on the number of OODs per 100 000 people for each of the 17 residential planning districts in Philadelphia for 2016. Residential planning districts with fewer than 30 OODs per 100 000 population were defined as not elevated (n = 174), districts with 30 to 49 OODs per 100 000 population were defined as elevated (n = 77), and districts with 50 or more OODs per 100 000 were defined as very elevated (n = 167).

Statistical Analysis

We reported proportions with 95% confidence intervals for naloxone availability and used Pearson χ^2 tests to compare differences by pharmacy and neighborhood characteristics. We reported medians with interquartile ranges (IQRs) for the cost of naloxone nasal spray. We used a significance value of 5% in all testing; *P* values reported are 2-sided. We conducted the statistical analysis using Stata statistical software version 15 (StataCorp)[10] and the geospatial analysis using ArcGIS geographic information system version 10.4 (Esri).[11]

Results

Among the 418 pharmacies surveyed, 60% were located in low-income neighborhoods and 55.0% were independent stores (**Table 1**). There were no substantial differences between participating and nonparticipating pharmacies by pharmacy and neighborhood characteristics (eTable 1 in the Supplement). One in 3 pharmacies (34.2%) had naloxone nasal spray in stock, with significant differences by pharmacy type and neighborhood characteristics. Naloxone was more likely to be in stock in chain stores (45.9%; 95% CI, 38.2%-53.7%) than in independent stores (27.8%; 95% CI, 22.4%-34.0%). Naloxone was less likely to be available in pharmacies located in predominately minority neighborhoods (28.8%; 95% CI, 21.8%-36.9%) compared with neighborhoods with a large

Table 1. Availability of Naloxone Nasal Spray at Pharmacies in Philadelphia, Pennsylvania, 2017

Characteristic	Total, No. (%)	Naloxone Nasal Spray Availability, No. (%) [95% CI, %]		*P* Value[a]
		Available	Not Available	
Overall	418 (100)	143 (34.2) [29.8-38.9]	275 (65.8) [61.1-70.2]	
Pharmacy type				
Chain	157 (37.6)	72 (45.9) [38.2-53.7]	85 (54.1) [46.3-61.8]	<.001
Independent	230 (55.0)	64 (27.8) [22.4-34.0]	166 (72.2) [66.0-77.6]	
Food store or mass retailer	31 (7.4)	7 (22.6) [11.0-40.8]	24 (77.4) [59.2-89.0]	
Neighborhood characteristics				
Minority population[b]				
Tertile 1: <41.8%	142 (34.4)	58 (40.8) [33.0-49.2]	84 (59.2) [50.8-67.0]	.10
Tertile 2: 41.8%-89.0%	132 (32.0)	44 (33.3) [25.8-41.9]	88 (66.7) [58.1-74.2]	
Tertile 3: >89.0%	139 (33.6)	40 (28.8) [21.8-36.9]	99 (71.2) [63.1-78.2]	
Not low income[b,c]	165 (40.0)	60 (36.4) [29.3-44.0]	105 (63.6) [56.0-70.7]	.49
Low income	248 (60.0)	82 (33.1) [27.5-39.2]	166 (66.9) [60.8-72.5]	
Planning district opioid overdose deaths (per 100 000 people)[d]				
Not elevated: <30	174 (41.6)	67 (38.5) [31.5-46.0]	107 (61.5) [54.0-68.5]	.30
Elevated: 30-49	77 (18.4)	24 (31.2) [21.8-42.4]	53 (68.8) [57.6-78.2]	
Very elevated: ≥50	167 (40.0)	52 (31.1) [24.5-38.6]	115 (68.9) [61.4-75.5]	

[a] Differences tested using χ^2 tests.

[b] Five pharmacies had missing neighborhood characteristics.

[c] Census tracts were defined as low income if at least 20% of the population had household incomes that were below the federal poverty level or if the median household income did not exceed 80% of the median household income in Philadelphia ($37 479).

[d] Medical Examiner's Office, Philadelphia Department of Public Health (2016).[8]

proportion of white residents (40.8%; 95% CI, 33.0%-49.2%). Pharmacies located in planning districts with very elevated rates of OOD were less likely to carry naloxone when compared with those with lower rates of OOD (31.1%; 95% CI, 24.5%-38.6% vs 38.5%; 95% CI, 31.5%-46.0%).

Among the 143 pharmacies that stocked naloxone, 61.5% (95% CI, 53.2%-69.2%) indicated it was available without a prescription (**Table 2**). Naloxone was more likely to be available without a prescription in chain stores (80.6%; 95% CI, 69.6%-88.2%) than in independent stores (42.2%; 95% CI, 30.6%-54.7%). Of the 275 pharmacies that did not have naloxone in stock, 70.5% (95% CI, 64.7%-75.7%) reported they were able to order it. While 91.8% (95% CI, 83.6%-96.1%) of chains reported they could order it, only 60.6% (95% CI, 52.8%-67.9%) of independents were able to do so. Predominately minority and low-income neighborhoods were less likely to offer naloxone without a prescription and less likely to be able to order it when compared with other neighborhoods. For example, only 51.2% (95% CI, 40.4%-62.0%) of pharmacies located in low-income neighborhoods offered naloxone without a prescription, compared with 75.0% (95% CI, 62.3%-84.5%) of pharmacies located in higher-income neighborhoods. Naloxone was less likely to be available without a prescription in neighborhoods that had elevated or very elevated rates of OOD when compared with neighborhoods with lower rates.

Similar patterns were observed when we examined the availability of naloxone by neighborhood characteristics for chain and independent pharmacies separately (eTable 2 and eTable 3 in the Supplement). For example, chains located in neighborhoods with very elevated rates of OOD were not only less likely to carry naloxone nasal spray (40.7% vs 46.8%) but were also less likely to offer it without a prescription (77.3% vs 86.1%) when compared with chains located in other neighborhoods.

The median (IQR) out-of-pocket cost for naloxone among pharmacies offering it without a prescription was $145 ($119-$150); costs of naloxone were greatest in independent pharmacies (median [IQR] cost, $147 [$140-$155]) and pharmacies located in planning districts with elevated rates (median [IQR] cost, $150 [$135-$150]) or very elevated rates (median [IQR] cost, $145 [$146-$150]) of overdose deaths (**Table 3**). In addition, 17.4% (95% CI, 10.7%-27.2%) of pharmacies that did not require a prescription required individuals to be aged 18 years or older to receive it. Such age restrictions were less common in neighborhoods with very elevated OOD rates (13.3%; 95% CI, 4.9%-31.3%).

The availability of naloxone nasal spray with or without a prescription at Philadelphia pharmacies is depicted in the **Figure**. Among the 5 planning districts with very elevated rates of OOD, there were notable differences in naloxone availability (eTable 4 in the Supplement). For example, 47.6% of pharmacies in the River Wards area stocked naloxone nasal spray, most of which (90%) offered it without a prescription. In contrast, in the Lower Far Northeast locality, 18.2% of pharmacies stocked naloxone, of which 50.0% offered it without a prescription.

Discussion

Despite the widespread implementation of naloxone access laws and important role of naloxone in preventing potentially fatal opioid overdoses, many barriers to its distribution and use remain.[12] Such barriers are particularly important in communities that have been especially affected by the epidemic and that experience high overdose rates, including in Philadelphia.[13] We conducted a telephone survey to examine the availability and cost of naloxone nasal spray among all retail pharmacies in Philadelphia in 2017. We found that despite the implementation of a statewide standing order in Pennsylvania more than 3 years prior to our study, only one-third of Philadelphia pharmacies carried naloxone nasal spray and many also required a physician's prescription. Our findings also suggest that communities with the highest rates of fatal opioid overdose may be less likely to have naloxone access through their local pharmacies.

Although Philadelphia persistently has among the highest rates of OOD in Pennsylvania,[13] our study indicates that barriers in accessing naloxone at local pharmacies are similar to those identified

Table 2. Prescription Requirements and Ability to Order Naloxone Nasal Spray at Pharmacies in Philadelphia, Pennsylvania, 2017

Characteristic	Prescription Required Among Pharmacies Stocking Naloxone Nasal Spray (n = 143), No. (%) [95% CI, %]				Ability to Order Among Pharmacies Not Stocking Naloxone Nasal Spray (n = 268), No. (%) [95% CI, %][a]			
	Total, No. (%)	Without a Prescription	With a Prescription	*P* Value[b]	Total, No. (%)	Able to Order	Unable to Order	*P* Value[b]
Overall	143 (100.0)	88 (61.5) [53.2-69.2]	55 (38.5) [30.8-46.8]		275 (100.0)	189 (70.5) [64.7-75.7]	79 (29.5) [24.3-35.3]	
Pharmacy type								
Chain	72 (50.3)	58 (80.6) [69.6-88.2]	14 (19.4) [11.8-30.4]		85 (30.9)	78 (91.8) [83.6-96.1]	7 (8.2) [3.9-16.4]	
Independent	64 (44.8)	27 (42.2) [30.6-54.7]	37 (57.8) [45.3-69.4]	<.001	166 (60.4)	97 (60.6) [52.8-67.9]	63 (39.4) [32.1-47.2]	<.001
Food store or mass retailer	7 (4.9)	3 (42.9) [12.8-79.3]	4 (57.1) [20.7-87.2]		24 (8.7)	14 (60.9) [39.7-78.6]	9 (39.1) [21.4-60.3]	
Neighborhood characteristics								
Minority population[c]								
Tertile 1: <41.8%	58 (40.8)	41 (70.7) [57.6-81.1]	17 (29.3) [18.9-42.4]		84 (31.0)	61 (73.5) [62.9-81.9]	22 (26.5) [18.1-37.1]	
Tertile 2: 41.8%-89.0%	44 (31.0)	25 (56.8) [41.7-70.7]	19 (43.2) [29.3-58.3]	.15	88 (32.5)	63 (73.3) [62.8-81.6]	23 (26.7) [18.4-37.2]	.20
Tertile 3: >89.0%	40 (28.2)	21 (52.5) [37.0-67.6]	19 (47.5) [32.4-63.0]		99 (36.5)	61 (64.2) [54.0-73.3]	34 (35.8) [26.7-46.0]	
Not low income[c,d]	60 (42.3)	45 (75.0) [62.3-84.5]	15 (25.0) [15.5-37.7]	.004	105 (38.7)	78 (75.0) [65.7-82.4]	26 (25.0) [17.6-34.3]	.09
Low income	82 (57.7)	42 (51.2) [40.4-62.0]	40 (48.8) [38.0-59.6]		166 (61.3)	107 (66.9) [59.2-73.8]	53 (33.1) [26.2-40.8]	
Planning district opioid overdose deaths (per 100 000 people)[e]								
Not elevated: <30	67 (46.9)	45 (67.2) [54.9-77.4]	22 (32.8) [22.6-45.1]		107 (38.9)	76 (73.8) [64.4-81.4]	27 (26.2) [18.6-35.6]	
Elevated: 30-49	24 (16.8)	13 (54.2) [34.1-73.0]	11 (45.8) [27.0-65.9]	.41	53 (19.3)	37 (69.8) [56.1-80.7]	16 (30.2) [19.3-43.9]	.72
Very elevated: ≥50	52 (36.4)	30 (57.7) [43.8-70.5]	22 (42.3) [29.5-56.2]		115 (41.8)	76 (67.9) [58.6-75.9]	36 (32.1) [24.1-41.4]	

[a] Seven pharmacies had missing information.

[b] Differences tested using χ^2 tests.

[c] One pharmacy had missing neighborhood characteristics.

[d] Census tracts were defined as low income if at least 20% of the population had household incomes that were below the federal poverty level or if the median household income did not exceed 80% of the median household income in Philadelphia ($37 479).

[e] Medical Examiner's Office, Philadelphia Department of Public Health (2016).[8]

by Graves et al[5] in other counties throughout the state. Our findings that independent pharmacies are less likely to stock naloxone and more likely to require a prescription to dispense it are also consistent with statewide estimates.[5] Although this prior report[5] did not observe differences across counties within Pennsylvania, our analyses indicate substantial variation in the availability and cost of naloxone across neighborhoods within Philadelphia. Importantly, we found that residents of

Table 3. Age Restrictions and Out-of-Pocket Cost Among Pharmacies That Offer Naloxone Nasal Spray Without a Prescription

Characteristic	Pharmacies, No.[a,b]	Out-of-Pocket Cost, Median (IQR), $	*P* Value[c]	Age Restriction, No. (%) [95% CI, %][d]	*P* Value[e]
Overall	86	145 (110-150)		15 (17.4) [10.7-27.2]	
Pharmacy type					
Chain	56	140 (110-150)		11 (19.6) [11.1-32.4]	
Independent	27	147 (140-155)	.02	4 (14.8) [5.5-34.3]	.98
Food store or mass retailer	3	110 (110-150)		0	
Neighborhood characteristics[f]					
Minority population					
Tertile 1: <41.8%	41	145 (130-145)		9 (22.0) [11.6-37.5]	
Tertile 2 41.8%-89.0%	24	145 (110-150)	.23	5 (20.8) [8.7-42.2]	.24
Tertile 3: >89.0%	20	142 (110-157)		1 (5.0) [0.6-29.9]	
Not low income[g]	44	143 (110-150)	.22	9 (20.5) [10.8-35.3]	.48
Low income	41	145 (130-150)		6 (14.6) [6.6-29.4]	
Planning district overdose mortality rate (per 100 000 people)[h]					
Not elevated: <30	44	140 (110-150)		11 (25.0) [14.2-40.2]	
Elevated: 30-49	12	150 (135-150)	.30	0	.14
Very elevated: ≥50	30	145 (136-150)		4 (13.3) [4.9-31.3]	

Abbreviation: IQR, interquartile range.

[a] One pharmacy had missing information on cost (N = 87).

[b] Two pharmacies had missing age restriction data (N = 86).

[c] *P* values based on statistical significance testing using Mann-Whitney *U* tests.

[d] Pharmacy restricted access to those aged 18 years or older and required identification before dispensing.

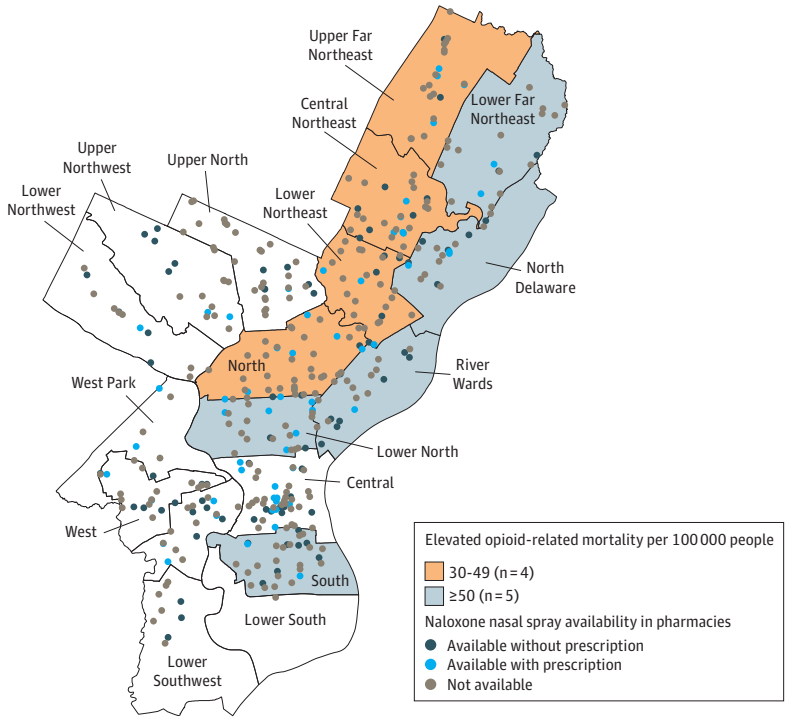
[e] *P* values based on χ^2 tests.

[f] One pharmacy had missing neighborhood characteristics.

[g] Census tracts were defined as low income if at least 20% of the population had household incomes that were below the federal poverty level or if the median household income did not exceed 80% of the median household income in Philadelphia, Pennsylvania ($37 479).

[h] Medical Examiner's Office, Philadelphia Department of Public Health (2016).[8]

Figure. Availability of Naloxone Nasal Spray at Pharmacies in Philadelphia, Pennsylvania, 2017



The map shows the location of Philadelphia pharmacies and availability of naloxone nasal spray (with or without a prescription required). Mortality data are from the Medical Examiner's Office, Philadelphia Department of Public Health (2016).[8] Data for naloxone nasal spray availability are from the National Council for Prescription Drug Programs (2015)[6] and a survey of all pharmacies in Philadelphia performed in 2017.

communities with the highest rates of OOD are more likely to encounter barriers in accessing naloxone at their local pharmacies.

Our findings suggest that naloxone access laws that consist of a statewide standing order are not necessarily more effective than laws that include more restrictive standing order protocols in expanding the availability of naloxone at local pharmacies. For example, when compared with Pennsylvania, more pharmacies in California, a state without a statewide standing order for naloxone, stocked naloxone nasal spray in 2017.[2,5] In addition, California pharmacies were only slightly less likely to offer naloxone without a prescription than Pennsylvania pharmacies.[2,5] These findings underscore the importance of increasing pharmacy awareness of statewide standing order protocols and ensuring naloxone is available in their stores.[5]

In response to concerns that pharmacies have failed to facilitate naloxone access, Philadelphia recently introduced a bill that will require all pharmacies to stock naloxone and post a sign notifying the public that naloxone is available in their stores.[14] Our study provides important baseline information prior to the implementation of this legislation and can be used to guide and target its enforcement, particularly in neighborhoods with the highest rates of fatal opioid overdose that also have disproportionately fewer pharmacies that carry naloxone. While mandating that pharmacies stock naloxone is important, our findings suggest that policies that discourage pharmacies from imposing unnecessary dispensing restrictions, including individual prescription or age requirements, are also critical in these neighborhoods, as are efforts that address the high cost of naloxone. Such efforts may include the distribution of naloxone nasal spray at no cost to laypersons living in low-income neighborhoods with high rates of overdose.[15]

Limitations

Our analysis has limitations. We only examined the availability of naloxone nasal spray and may therefore underestimate naloxone availability. We focused on the intranasal naloxone formulation because it is widely used and considered the most convenient and easy-to-use option, in particular for laypersons.[16,17] Its use has increased substantially since it was first approved by the US Food and Drug Administration in November 2015; in 2017 naloxone nasal spray accounted for nearly 70% of all naloxone prescriptions dispensed in the United States.[16] In addition, the vast majority of naloxone formulations stocked at retail pharmacies in Pennsylvania are for the nasal spray.[5] State policies and pharmacy practice continue to evolve in response to the epidemic, but pharmacies were surveyed at 1 point in time. Although policies aimed at improving naloxone availability at pharmacies have not changed since the statewide standing order was first implemented in August 2015, since our survey was conducted, Philadelphia has implemented a series of additional programs, including a mass media campaign that started in early 2018, encouraging the public to get and keep naloxone in their homes.[18]

Conclusions

This study suggests that efforts to strengthen the implementation of statewide standing orders for naloxone and better ensure its supply at local pharmacies are warranted, especially in communities with the highest rates of OOD.

ARTICLE INFORMATION

Accepted for Publication: April 23, 2019.

Published: June 7, 2019. doi:10.1001/jamanetworkopen.2019.5388

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Statistical analysis: Guadamuz, Qato.

Obtained funding: Qato.

Administrative, technical, or material support: Chaudhri, Trotzky-Sirr, Qato.

Supervision: Qato.

Conflict of Interest Disclosures: Dr Alexander reported serving as chair of the US Food and Drug Administration's Peripheral and Central Nervous System Advisory Committee; serving as a paid advisor to IQVIA; performing consulting for and holding equity in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and membership on OptumRx's National Pharmacy and Therapeutics Committee. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. Dr Chaudhri reported employment as a postdoctoral fellow in the Division of Global Regulatory Affairs of UCB Inc. Dr Qato reported serving as a paid consultant for the Public Citizen's Health Research Group. No other disclosures were reported.

Funding/Support: Ms Guadamuz was supported, in part, by the Robert Wood Johnson Foundation Health Policy Research Scholar program and by the National Heart, Lung, and Blood Institute grant T32-HL125294. Dr Qato was supported, in part, by the Robert Wood Johnson Foundation as part of the Clinical Scholars Leadership program.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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SUPPLEMENT.

eFigure. Pharmacy Selection
eTable 1. Characteristics of Pharmacies by Response/Survey Status
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Appendix I-10

Letters

RESEARCH LETTER

Provision of Naloxone Without a Prescription by California Pharmacists 2 Years After Legislation Implementation

Layperson access to the opioid overdose reversal medication naloxone can reduce mortality.[1,2] Legislation in California has allowed trained pharmacists to furnish naloxone without a physician's prescription since January 27, 2016.[3] Under a Board of Pharmacy protocol, naloxone is available by patient request or pharmacist suggestion. A furnishing pharmacist is required to screen and educate patients on opioid overdose prevention, recognition, and response. With patient consent, the pharmacist must notify the primary physician that naloxone was furnished. We estimated the availability of pharmacist-furnished naloxone 2 years after implementation.

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Methods | The Office for Human Research Protections at Claremont Graduate University deemed this study nonhuman research. An anonymous telephone survey of a 20% random sample of California community pharmacies was conducted between January 23 and February 28, 2018. The California State Board of Pharmacy website was accessed on January 2, 2018, to identify all licensed California pharmacies, excluding pharmacies with canceled, revoked, probationary, or restricted licenses and hospital, correctional, or specialty pharmacies. Thirty trained interviewers posed as potential customers. Using a standardized script, they asked any pharmacy staff: "I heard that you can get naloxone from a pharmacy without a prescription from your doctor. Can I do that at your pharmacy?" If the response was affirmative, they asked what formulations were available, the cash price, and whether naloxone could be billed to insurance. Additional unsolicited information was recorded.

Proportions with 95% confidence intervals, medians with interquartile ranges (IQRs), and χ^2 tests comparing differences in availability by urbanity (census tract designation) and pharmacy type (independent or chain, defined as ≥5 locations) were estimated using Stata version 15.1 (StataCorp). With a power of 85% and $\alpha = .05$, the sample size required to detect an effect size of 0.1 in χ^2 tests comparing differences in availability by urbanity and pharmacy type was n = 898. Statistical significance was set at a 2-tailed $P < .05$.

Results | Of 6962 California pharmacies, 6047 were eligible, 1209 were surveyed, and data were collected from 1147 (93.3%). Most pharmacies were urban (98.7%) and part of a chain (66.2%) (**Table 1**). Pharmacist-furnished naloxone was available at 23.5% (95% CI, 21.0%-26.0%) of pharmacies. Differences by urbanity were not statistically significant, although rural pharmacies were underrepresented. There was a significant difference by pharmacy type, with 31.6% (95% CI, 28.3%-35.1%) of chain pharmacies compared with 7.5% (95% CI, 5.1%-10.6%) of independent pharmacies furnishing naloxone ($P < .001$).

Among pharmacies furnishing naloxone (n = 269), 225 (83.6%) offered a nasal formulation (**Table 2**). Fourteen (5.2%) offered combination buprenorphine-naloxone tablets used for treatment of opioid use disorder, not opioid overdose. Of pharmacies furnishing naloxone, 50.6% had nasal naloxone in stock. Chain pharmacies were significantly more likely to have nasal naloxone in stock (52.3%; 95% CI, 46.3%-59.4%) compared with independents (31.0%; 95% CI, 15.3%-50.8%) ($P = .03$). Regarding insurance billing,

Table 1. Availability of Naloxone Without a Physician's Prescription in California Pharmacies[a]

	No. (%) [95% CI]			
	All Pharmacies	Pharmacist-Furnished Naloxone Available[b]	Pharmacist-Furnished Naloxone Not Available	*P* Value[c]
Overall	1147 (100.0)	269 (23.5) [21.0-26.0]	878 (76.5) [74.0-79.0]	
Pharmacy type				
Chain	759 (66.2) [63.4-68.9]	240 (31.6) [28.3-35.1]	519 (68.4) [64.9-71.7]	<.001
Independent	388 (33.8) [31.1-36.6]	29 (7.5) [5.1-10.6]	359 (92.5) [89.4-94.9]	
Setting[d]				
Urban/urban cluster	1132 (98.7) [97.9-99.3]	263 (23.2) [20.8-25.8]	869 (76.8) [74.1-79.2]	.13
Rural	15 (1.3) [0.7-2.2]	6 (40) [16.3-67.7]	9 (60) [32.3-83.7]	

[a] There were 1209 sampled pharmacies available for inclusion. Data were not collected from 62 sampled pharmacies for the following reasons: closed door (n = 33), permanently closed (n = 6), specialty pharmacy (n = 5), medical supply (n = 5), no contact after 3 attempts (n = 4), part of closed health center (n = 3), no working telephone number (n = 2), pet pharmacy (n = 2), mail order (n = 1), and telepharmacy (n = 1).

[b] Survey question: "I heard that you can get naloxone from a pharmacy without a prescription from your doctor. Can I do that at your pharmacy?"

[c] By Pearson χ^2 test for independence.

[d] Urbanity was determined using the *2010 Census of Population and Housing*.[6]

Table 2. Characteristics of Naloxone Without a Physician's Prescription in California Pharmacies[a]

Characteristics	Estimate	*P* Value[b]
Pharmacies offering pharmacist-furnished naloxone, No. (%) [95% CI] (n = 269)		
Nasal naloxone offered	225 (83.6) [78.7-87.9]	
Auto-injector offered	19 (7.1) [4.3-10.8]	
Other formulations offered[c]	70 (26.0) [20.9-31.7]	
Nasal naloxone in stock	136 (50.6) [44.4-56.7]	
Chain (n = 240)	127 (52.3) [46.3-59.4]	.03
Independent (n = 29)	9 (31.0) [15.3-50.8]	
Able to bill insurance	161 (59.9) [53.7-65.8]	
Chain (n = 240)	143 (59.6) [53.1-65.8]	.64
Independent (n = 29)	18 (62.1) [42.3-79.3]	
Pharmacies providing cost information (n = 203)		
Cash cost of nasal formulation, median (IQR), $	136 (123.5-146)	
Chain (n = 184)	136 (120-143.5)	.04
Independent (n = 19)	150 (138.5-170)	

Abbreviation: IQR, interquartile range.

[a] Survey questions: "What formulations of naloxone are available?"; "What is the cost if I want to pay cash?"; "Can you bill insurance for this?"; "Do you have Narcan nasal spray in stock right now?"

[b] By Pearson χ^2 test for independence.

[c] Fourteen pharmacies (5.2% of 269) offered buprenorphine-naloxone combination products as a potential formulation option.

59.9% of pharmacies replied correctly that pharmacist-furnished naloxone could be billed, with no significant difference by pharmacy type. The median cash price of nasal naloxone (pack of 2) at chain pharmacies was $136 (IQR, $120-$143.50) compared with $150 (IQR, $138.50-$170) (*P* = .04) at independents.

A number of erroneous statements were made by respondents, including that naloxone was a controlled substance, that a tablet formulation was available, and that injectable formulations not appropriate for layperson use were available.

Discussion | Two years after implementation, only 23.5% of a representative sample of California retail pharmacies were furnishing naloxone to patients without a physician prescription. Reasons the practice was not being implemented may include lack of knowledge of legislation, lack of required training, stigma about substance use disorder, and time.[4,5] With only 50.6% of pharmacies stocking nasal naloxone, patients may face a delay in access to the drug.

Limitations include low rural pharmacy representation, inclusion of nonpharmacist respondents, absence of data on reasons why pharmacies were not furnishing naloxone, and restriction to California, although most states have some form of pharmacy-based naloxone distribution. Over the last 2 years, the Board of Pharmacy has provided naloxone training to more than 700 of California's 40 000 pharmacists. Whether naloxone will become more available with training of additional pharmacists and implementation of standardized policies by pharmacy chains needs to be studied.

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Accepted for Publication: July 31, 2018.

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Drafting of the manuscript: Puzantian.
Critical revision of the manuscript for important intellectual content: Both authors.
Statistical analysis: Puzantian.
Administrative, technical, or material support: Both authors.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Additional Contributions: We thank Chris Lim, BS, Howard Park, BS, and Rachita Sumbria, PhD, all from Keck Graduate Institute, for performing statistical analyses, a role for which they did not receive compensation; and Ramisha Ali, BS, Inet Amirian, BS, Kofi Atta-Boateng, BS, BSc, Priscilla Arteaga, BS, Winnie Chan, BS, Allen Chung, BS, Anthony Costy, BS, Nour Dabbas, BS, Sirun Gasparyan, BS, Marina Girgis, BA, Dominic Goria, BS, Shana Henderson, BS, Amandeep Kaur, BS, Tanya Lengvilas, BS, Chris Lim, BS, Mark Lua, BS, Hollie Maguire, BS, Dominique Miller, MS, Conor Moldowan, BS, Amarachi Okafor, BS, Rupangi Patel, MS, Tiffany Samouha, BS, Patricia Sedlock, BS, Sara Sheik, BA, Michael Soliman, BA, Taguhi Tagakchyan, BS, Emily Tat, BA, Danielle Tessier, BS, Peter Tran, BS, and Rebekah Trules, MPH, all from Keck Graduate Institute, for conducting telephone interviews, a role for which they did not receive compensation.

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Naloxone Accessibility Without a Prescriber Encounter Under Standing Orders at Community Pharmacy Chains in Texas

In response to the opioid overdose epidemic, each US state has passed legislation to expand access to naloxone, the opioid overdose antidote.[1] Although naloxone access laws

Appendix I-11

Drug and Alcohol Dependence 188 (2018) 187–192

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Predicting pharmacy naloxone stocking and dispensing following a statewide standing order, Indiana 2016

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ARTICLE INFO

Keywords:
Naloxone access
Opioid overdose reversal
Pharmacy practice
Public health law

ABSTRACT

Background: While naloxone, the overdose reversal medication, has been available for decades, factors associated with its availability through pharmacies remain unclear. Studies suggest that policy and pharmacist beliefs may impact availability. Indiana passed a standing order law for naloxone in 2015 to increase access to naloxone.

Objective: To identify factors associated with community pharmacy naloxone stocking and dispensing following the enactment of a statewide naloxone standing order.

Methods: A 2016 cross-sectional census of Indiana community pharmacists was conducted following a naloxone standing order. Community, pharmacy, and pharmacist characteristics, and pharmacist attitudes about naloxone dispensing, access, and perceptions of the standing order were measured. Modified Poisson and binary logistic regression models attempted to predict naloxone stocking and dispensing, respectively.

Results: Over half (58.1%) of pharmacies stocked naloxone, yet 23.6% of pharmacists dispensed it. Most (72.5%) pharmacists believed the standing order would increase naloxone stocking, and 66.5% believed it would increase dispensing. Chain pharmacies were 3.2 times as likely to stock naloxone. Naloxone stocking was 1.6 times as likely in pharmacies with more than one full-time pharmacist. Pharmacies where pharmacists received naloxone continuing education in the past two years were 1.3 times as likely to stock naloxone. The attempted dispensing model yielded no improvement over the constant-only model.

Conclusions: Pharmacies with larger capacity took advantage of the naloxone standing order. Predictors of pharmacist naloxone dispensing should continue to be explored to maximize naloxone access.

1. Introduction

Opioids have become a national priority in the United States, largely because opioid overdose (OOD) is now a leading cause of death for Americans under 50 years of age (CDC, 2017a,b). The rate of OOD quadrupled between 1999 and 2015 and reached a point where 91 Americans died daily (CDC, 2017a). Part of the federal government's response was to identify access to the OOD reversal medication naloxone as part of a tripartite approach to reducing OOD (Kim et al., 2016).

Recently, state statutes and regulations expanded prescribing and dispensing authority to increase naloxone access (Davis and Carr, 2015; Prescription Drug Abuse Policy System, 2017). In some states, naloxone can now be dispensed without a medical license and a prescription (Davis and Carr, 2017). As of this writing, all but three states have enacted legislation allowing others, beyond first responders or medical professionals, to distribute and/or administer naloxone (The Network for Public Health Law, 2016; Davis and Carr, 2017). Such legal

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https://doi.org/10.1016/j.drugalcdep.2018.03.032
Received 27 October 2017; Received in revised form 21 February 2018; Accepted 8 March 2018
Available online 26 April 2018

approaches equip communities with a powerful tool to save lives of those experiencing OOD.

Community pharmacies are primary partners in naloxone distribution (Nielsen and Van Hout, 2016). This is especially true for communities burdened with high need and low levels of public health resource because pharmacies are ubiquitous, staffed with professionals trained in medication therapy management, and are often perceived as non-stigmatizing and normalizing (Amesty et al., 2012; Lutnik et al., 2012; Meyerson et al., 2013). Though, as Zaller et al. suggested, there may be perceptions among people who inject drugs (PWID) that pharmacy staff would be stigmatizing (2013). Pharmacies may play an even greater public health role, particularly for PWID, due to the paucity of public health resources for PWID health. This is definitely the case in Indiana, where syringe access policy has met several barriers (Meyerson et al., 2017).

While few pharmacies stocked naloxone as recently as 2009 (Hammett et al., 2014), a ten-fold dispensing increase occurred in retail pharmacies from 2013 to 2015 (Jones et al., 2016). Given the potential for pharmacies to help reduce OOD, there is growing interest in understanding their precise role in naloxone access, whether that of education, consultation, dispensing, or identification of likely naloxone beneficiaries (Bailey and Wermeling, 2014; Freeman et al., 2017). This is especially important for services to PWID given the potential for stigma (Zaller et al., 2013; Hammett et al., 2014; Green et al., 2017b).

Like many U.S. communities, Indiana's struggle with opioid addiction is compounded by a dearth of public health resources (Trust for America's Health, 2016). Uniquely, in 2015, Indiana was the location of the largest HIV outbreak in decades associated with injection drug use (Conrad et al., 2015). That year, in recognition of persistent OOD, Indiana enacted law to increase access to an "overdose intervention drug," called naloxone, by permitting prescribing and dispensing without a medical exam and without patient-specific prescriptions through standing orders issued by health care providers (P.L. 32-2015). The following year, the statute was amended to require that the State Department of Health "ensure that a statewide standing order.... is issued" (P.L. 6-2016). The Department of Health established a process in which individuals and entities that dispense, administer, or acquire naloxone can register annually online as required under the statutory code (Ind. Code 16-42-27-2(e)(1)). Registered dispensing entities can distribute naloxone to opioid users, family members, friends, or other individuals or entities to help prevent OOD. Six other U.S. states (MD, NC, NM, PA, TX, WY) have similar state-wide standing order laws (Davis and Carr, 2017), and over 40 states have non-patient specific standing orders (Davis and Carr, 2017; Hawk et al., 2015). In Indiana, naloxone entities must provide education and training about naloxone, how to use it, and to call 9-1-1 immediately before administering it. Entities must also provide addiction treatment information and referrals to treatment programs (Ind. Code 16-42-27-2(a)).

Within four months of Indiana's 2015 standing order enactment, only 4 Indiana pharmacies registered with the state as dispensing naloxone (Smith, 2015). A rapid 21-month increase in community pharmacy registration occurred: by 2016, 347 dispensing entities were registered with the state, and by October 2017, 452 community pharmacies were registered entities (Indiana State Department of Health, 2015). At face value, one might suppose the standing order facilitated pharmacy naloxone stocking and dispensing. One might also suppose that registration as a naloxone entity meant that the pharmacies actually stocked naloxone. These suppositions are as yet unclear, as are questions about other determinants of pharmacy naloxone stocking and dispensing.

Studies among pharmacists elsewhere have attempted to understand naloxone dispensing, but this is especially true for those when naloxone was available only via prescription. Raisch et al.'s small study of pharmacists in seven states found general support for naloxone dispensing with a prescription (Raisch et al., 2005), yet Hammett's review of studies from six countries (including the U.S.) found barriers to dispensing including legality perceptions, store chain practice/policy, and pharmacist stigmatizing attitudes (Amesty et al., 2012; Hammett et al., 2014). Zaller's 2013 study among Rhode Island pharmacy staff and PWID found support among pharmacists and PWID for a naloxone pharmacy intervention, though it clearly indicated the need for pharmacist education about naloxone (Zaller et al., 2013). Two studies found general support for dispensing naloxone but discomfort with actively identifying patients who might benefit from it (Bailey and Wermeling, 2014) and concerns about confidentiality (Zaller et al., 2013).

A more robust 2015 study among Kentucky pharmacists found that 54.0% were willing to dispense with a valid prescription; however, community pharmacists were more concerned than those in other practice settings with the frequency of pharmacy visits by customers seeking naloxone and with Kentucky's collaborative practice policy implementation (Freeman et al., 2017). That same year, a study by Green et al. among Massachusetts and Rhode Island pharmacists echoed concerns over dispensing logistics and included concerns about opioid safety management (Green et al., 2017a,b). Other studies report continued discomfort dispensing naloxone without a prescription. A 2016 West Virginia study found that only 20.4% of community pharmacists were comfortable dispensing naloxone without a prescription (Thornton et al., 2017). That same year, Nielsen et al.'s Australian study found that while 90.3% were willing to dispense naloxone with a prescription, only 40.8% were willing to dispense without one (Nielsen et al., 2016). Unfortunately, none of these studies associated attitudes with reported dispensing behaviors.

As these pharmacy-based naloxone studies happened during earlier periods of state policy evolution, our understanding remains limited regarding factors associated with pharmacy naloxone stocking and dispensing under a statewide standing order. Thus, we sought to understand the perceived impact of the Indiana standing order and to identify salient factors associated with pharmacy naloxone stocking and dispensing.

2. Materials and methods

A cross-sectional census of managing pharmacists in Indiana's 850 community pharmacies was conducted from July-September 2016. The sample was identified by a match of licensed managing pharmacists provided by the Indiana Board of Pharmacy (February 2016) with retail pharmacies provided by Hayes Directories, Inc. (December 2015, Mission Viejo, CA).

The study used an online survey platform. Survey invitations were mailed by post directly to each managing pharmacist at their pharmacy and included an initial letter, study description, a survey link with a QR code for smartphone access, and a $5 bill as a pre-incentive. Two cycles of follow-up occurred with non-respondents (Agley et al., 2017). The study was deemed exempt by the Indiana University IRB.

Survey items included questions about pharmacist demographics, practice settings, pharmacy policy and practice, pharmacist education and practice, attitudes about and comfort levels regarding naloxone stocking and dispensing, and beliefs about the role of pharmacists in HCV and HIV prevention, treatment, and in the health of people who inject drugs (PWID). A focus was on PWID because of the tremendous need by this sub-population of opioid users for public health services, as demonstrated by Indiana's HIV outbreak and the lack of clarity about stigma towards PWID from pharmacists. The survey also asked pharmacists their beliefs about the impact of the recently enacted standing order. Finally, pharmacists indicated whether they had been asked by customers, medical professionals (nurses or physicians), or other pharmacists about naloxone during the past 2 years.

The survey was assessed for face validity and revised by a team of cross-disciplinary experts based on a pre-test with a small sample (n = 5) of non-managing pharmacists using trigger questions to assess comprehension, information retrieval, and judgment/recall. Survey

data were matched with the most recent available county-level secondary data describing community level markers for naloxone need: opioid overdose mortality rates (2002–2013) (Indiana State Epidemiologic Outcomes Working Group, 2014), medical underservice area designation (HRSA, 2016), and county progress toward syringe exchange policy adoption (Meyerson et al., 2017). These served as surrogate indicators of community need together with whether a pharmacist was asked by customers, pharmacists, or other medical professionals about naloxone. The use of OOD mortality rates as a community need indicator has precedent (Stopka et al., 2017). The use of medical underservice area indicated the need for health services generally in a community and the unique role a pharmacy might play in the health of the population. Finally, whether pharmacists were asked about naloxone was a recommendation of the research team's pharmacy practice members, based on their experience that community need is often indicated at the community pharmacy counter.

Outcomes of interest included pharmacy naloxone stocking and pharmacist dispensing. Naloxone stocking was measured by the question: "Does your pharmacy currently stock Naloxone, the opioid overdose reversal medication?" Pharmacist naloxone dispensing was measured by the question: "Have you dispensed Naloxone to patients/customers in your current pharmacy?"

Based on pharmacy naloxone studies, we hypothesized that the standing order would be associated with pharmacy naloxone stocking and pharmacist dispensing. Because stocking and dispensing was not evaluated prior to the law's implementation, we used pharmacist perceptions as proxy variables, asking: "Indiana now has a standing order for Naloxone" (a) "Does this policy increase the likelihood that your pharmacy will stock Naloxone?" and (b) "Does this policy increase the likelihood that you and your pharmacy staff will dispense Naloxone?"

At the community level, we hypothesized that pharmacies experiencing inquiries about naloxone in the past 2 years would be more likely to stock and dispense it. This was measured by the question: "In the last 2 years, have you or your pharmacy staff been asked about naloxone for the prevention of opioid overdose?" Responses were dummy coded as 'Asked by any of those groups/Not asked by any of those groups.' We also suspected that pharmacy type (e.g., chain, mass merchandising, food store, or independent) might affect stocking and dispensing practices, as might the number of pharmacists working at a given location.

At the individual/pharmacy level, we hypothesized that pharmacies would be more likely to stock and dispense naloxone if pharmacists themselves were comfortable dispensing it. Specifically, we asked about scenarios listed in Table 1. These scenarios were developed by our research team based on likely and legal scenarios and were grounded in pharmacy experience by three of the research team members (Shannon, Ryder, and Ritchie). Responses were dummy coded as 'Comfortable with any of the options listed above/Any other response.' Finally, we hypothesized that pharmacies would likely stock naloxone if managing pharmacists received continuing education about 'Naloxone for opioid overdose reversal' in the last 2 years.

To model pharmacist naloxone dispensing, we included two independent variables not incorporated in the stocking model: 1) whether the pharmacy stocked naloxone, and 2) pharmacist perception of their role as resources for PWID health. This was measured with the item: "Pharmacists/pharmacies are an important resource for injection drug users who may not have access to healthcare in the community." Response options were: *Strongly agree, Somewhat agree, Neither agree nor disagree, Somewhat disagree,* and *Strongly disagree*, and they were dummy coded as 'Somewhat or strongly agree/Neutral, disagree, or strongly disagree.'

The primary analysis was intended to be binary logistic regression models and estimation of odds ratios (SPSS v.24). However, calculating relative risk is more appropriate than calculating adjusted odds ratios when the outcome is common (Greenland, 2004). Thus, because more than half of pharmacies stocked naloxone, the analysis for pharmacy stocking naloxone (SAS v 9.4) was accomplished using a modified Poisson approach to estimate the relative risk and confidence intervals by using robust error variances (Zou, 2004). We retained the binary logistic regression approach for pharmacist naloxone dispensing. A single variable regression model was also run to test whether perception about the standing order would predict naloxone stocking and dispensing. Variables were dummy coded to avoid model overspecification. Prior to running each model, sets of predictor variables were tested for multicollinearity using an exclusion cut-off of VIF = 2.5 or higher (Midi et al., 2010).

Table 1
Community Pharmacy and Managing Pharmacist Characteristics, Indiana 2016 (N = 284).

Pharmacist characteristics and behavior	
Gender (Female)	143 (50.4%)
Race/ethnicity (White, non-Hispanic)	263 (92.6%)
Age	μ = 42.43 (r:25–73), SD:11.7
Years in practice	μ = 17.1 (r:1–51), SD:12.0
PharmD Degree	171 (60.2%)
Received Continuing Education about Naloxone in the past 2 years	172 (60.6%)
Pharmacy Practice Environment	
Type of pharmacy	
Chain	160 (56.3%)
Food store	64 (22.5%)
Mass merchandiser	49 (17.3%)
Independent	11 (3.9%)
Number of full time licensed pharmacists	μ = 2.24 (SD:1.11)
Pharmacy currently stocks Naloxone	165 (58.1%)
Pharmacist asked by customers or medical providers about Naloxone in the past 2 years	147 (51.8%)
Pharmacist Beliefs	
Standing order policy will increase likelihood that my pharmacy will stock Naloxone	206 (72.5%)
Standing order policy will increase the likelihood that I and my pharmacy staff will dispense Naloxone	189 (66.5%)
I am comfortable dispensing Naloxone to:	
A family member of someone who injects opiates	93 (32.7%)
An adult friend of someone who injects opiates	80 (28.2%)
A person who injects opiates, but only if they are not requesting to purchase it repeatedly	58 (20.4%)
A person who injects opiates even if they seek to purchase it repeatedly	30 (10.6%)
A teenager (15–17 yrs of age) who is a friend of someone who injects opiates	26 (9.2%)
Any of the people in the listed scenarios (above)	136 (47.9%)
I am not comfortable dispensing naloxone to any of these people (above)	52 (18.3%)
Pharmacists can be an important resource for injection drug users who may not have access to healthcare in the community (Generally agree)	218 (76.8%)

3. Results

3.1. Descriptive statistics

The study included 284 full responses for a response rate of 33.4% (see Table 1). The sample was primarily white, non-Hispanic, and evenly split by gender. Over half (60.6%) of pharmacists reported receiving continuing education about naloxone in the past 2 years.

Chain pharmacies were practice locations for 56.3% of pharmacists, which generally mirrored Indiana's distribution of pharmacies. Respondents practiced in 72.8% of Indiana counties, and 78.5% were located in areas with populations > 250,000 (not shown in table).

A majority of pharmacists (72.5%) believed that the newly enacted naloxone standing order would increase the likelihood of their pharmacy stocking naloxone. Slightly fewer (66.5%) believed it would increase the likelihood that they or their staff would dispense it; however,

Table 2
Modified Poisson Model: Indiana Pharmacy Stocks Naloxone (Yes) (N = 284), 2016.

Independent Variables	Parameter Estimate	Sig.	Adjusted Relative Risk (ARR)	95% CI for ARR
Chain Pharmacy (Yes)	1.18	< 0.0001	3.24	2.29–4.58
Received CE on Naloxone, Past 2 Years (Yes)	0.23	0.019	1.26	1.04–1.52
Asked About Naloxone by Any Group (Yes)	0.14	0.155	1.15	0.95–1.39
Comfortable Dispensing Naloxone (Yes)	0.07	0.337	1.07	0.93–1.23
Standing Order (More Likely to Stock)	0.16	0.199	1.17	0.92–1.48
More than One Full-Time Licensed Pharmacists	0.47	0.002	1.61	1.19–2.17

both sentiments were highly correlated, $r(282) = 0.7$, $p < .001$.

Less than half of pharmacists (47.9%) were comfortable dispensing naloxone in any of the scenarios listed in Table 1, even as 76.8% agreed that pharmacists can be an important resource for PWID who may not have access to healthcare in the community.

3.2. Regression model: Pharmacy stocking naloxone

Just over half (58.1%) of pharmacies stocked naloxone. A test of the full regression model with all six predictor variables against a constant-only model indicated an improvement in model fit according to change in quasi-likelihood under the independence model criterion (QIC) from 1212.9 to 1129.3. No predictor variable exceeded a VIF of 2.5.

As shown in Table 2, chain pharmacies were 3.2 times as likely to stock naloxone compared to other types of pharmacies (in aggregate), and pharmacies with more than one full-time licensed pharmacist were 1.6 times as likely to stock naloxone compared to those with one full-time pharmacist. In addition, pharmacies where the managing pharmacist had received continuing education on naloxone within the past 2 years were 1.3 times as likely to stock naloxone compared to those where that was not the case. No other predictor variables significantly contributed to the model.

Based on the theoretical importance of the standing order in Indiana, a single-variable regression model was also run with stocking naloxone as the dependent variable and perception of the standing order as the sole predictor variable. In the single-variable model, the perception that the standing order made it more likely that a pharmacy would stock naloxone was a significant predictor (unadjusted relative risk = 2.0, 95% CI: 1.5–2.7), but, as noted, it became non-significant when included in the full model.

3.3. Regression model: Pharmacist naloxone dispensing

While over half of pharmacies stocked naloxone, and a majority of pharmacists held beliefs supportive of naloxone's benefit for PWID health, only 23.6% of managing pharmacists dispensed it at their current pharmacies. A test of the full regression model with all seven predictor variables against a constant-only model was significant ($x^2 = 45.0$, $p < 0.001$), and −2LL improved from 310.3 to 265.3. The Hosmer and Lemeshow Goodness-of-Fit Test was not violated ($p = .8$). None of the predictor variables exceeded a VIF of 2.5. Correct classification by the constant-only model with a cut value of 0.500 was 76.4% (with 0% of the pharmacists personally dispensing naloxone correctly identified), while the full model correctly classified 77.5% of cases (with 4.5% of pharmacists personally dispensing naloxone correctly identified). This was an unimpressive improvement.

In the full model, only two independent variables were significant: pharmacists being asked about naloxone by any group (B = 1.1, AOR = 3.0, $p = .002$, 95% CI: 1.5–6.0) and the pharmacy currently stocking naloxone (B = 1.6, AOR = 4.8, $p = .001$, 95% CI: 1.9–12.3). As before, a single-variable regression model was also run with having dispensed naloxone as the dependent variable and perception of the standing order as the sole predictor variable. This model did not yield any improvements over the constant-only model.

4. Discussion

This study advanced our understanding of factors predicting pharmacy naloxone stocking; however, it was unable to do so for naloxone dispensing. The selected independent variables explained a large and significant portion of variance in whether a community pharmacy stocked naloxone, and the primary factors were type of pharmacy (chain), having more than 1 full-time pharmacist, and that the managing pharmacist receive continuing naloxone education within the past 2 years. However, the proxy measure of the standing order's impact, while significant in a standalone regression model, did not contribute significantly in the full model. Further, dispensing naloxone seemed to have almost entirely different predicting variables than stocking. As noted, a paucity of research has investigated the interplay between these variables. We offer some provisional assessments based on our findings to guide future studies.

First, prior to this study, there was evidence that more pharmacies began to stock naloxone after the implementation of the state standing order. Interpreted in isolation, pharmacist belief that the standing order might increase naloxone stocking was associated with naloxone stocking. However, the full model suggested that the standing order's contribution to variance in stocking naloxone was subsumed by structural aspects, especially the type of pharmacy and the number of full-time pharmacists. Thus, it may be the case that while state law facilitated naloxone stocking, one or more factors shared by larger and/or more systematized pharmacies was important in determining who stocked it. It is unclear whether this finding represented organizational capacity for change, such as tolerance for fiscal risk of a large-scale practice modification suggested by Doucette et al. (2012); whether it represented differential approaches to government policy by larger pharmacy groups, as suggested by Roberts et al. (2005); or whether it was the result of some other underlying factor such as the cost of naloxone as observed by Zaller et al. (2013). This last point is important because pharmacies must charge the full cost of naloxone. Even as cost reduction options exist, such as naloxone coupons, it is not clear how widespread such coupons are and who has access to them. Further, there are other naloxone distributors such as public health related programs, schools, or first responders; all of which might have access to subsidized or even free naloxone through grants and can therefore distribute it at significantly reduced cost or free of charge. While we are aware of these grants for naloxone distribution in Indiana and elsewhere, the geographic extent and adequacy of such subsidized access is not yet clear.

Individual-level indicators, such as having been asked about naloxone by any group and comfort dispensing naloxone, did not significantly predict whether a pharmacy stocked it. We cannot yet determine whether this is because naloxone stocking is simply not affected by managing pharmacists or because individual managing pharmacists have less autonomy in large, chain pharmacies than they do in smaller pharmacies regardless of their comfort levels with naloxone or the degree to which they have been asked about it by community and medical/pharmacy colleagues. That said, if pharmacy type and capacity facilitated naloxone stocking, it is also possible that managing pharmacists at these locations would not necessarily dispense it. Perhaps other pharmacists did. To learn this, a representative sample

would need to be drawn from all practicing community pharmacists to avoid selection bias.

The variables that we identified did not predict whether an individual managing pharmacist dispensed naloxone with meaningful accuracy. Further, the improvement of correct classification was largely driven by whether the pharmacy stocked naloxone, which is a logical dispensing requirement. Still, fewer than half of community pharmacies stocking naloxone also had a managing pharmacist who dispensed it. Dispensing naloxone is an individual behavior, yet it is admittedly curious that dispensing had not occurred at the majority of community pharmacies. Prior research indicates that lack of dispensing might be related to factors such as negative patient profiling (Drainoni et al., 2016) or more generalized stigma related to naloxone (Zaller et al., 2013; Green et al., 2017b; Penm et al., 2017). It is not clear that education is necessarily the solution because dispensing practices in our model were not related to pharmacist perception about the importance of PWID health and pharmacist naloxone continuing education. One possibility is that dispensing behavior may partly be driven by customers rather than by pharmacists – one cannot dispense something if one is not asked for it. Additionally, if one is asked but the price is prohibitive, the customer declines to purchase. While off-label use of injectable naloxone for intranasal administration can be relatively low-cost (approximately $40), Narcan nasal spray cost $150 per two-dose pack in 2016, while the Evzio auto-injector two-pack cost $4500 that same year (Gupta et al., 2016). Insurance coverage for naloxone may also be at issue. Indiana Medicaid covers naloxone under the statewide standing order, though it is not clear whether and how well private insurers cover it.

These findings lead to several follow-up questions and comments. First, this study suggests that large chain pharmacies were more likely to stock naloxone, and pharmacy type and size shared significant explanatory space with the standing order. One emerging unknown, then, is what steps can be taken to support naloxone stocking in smaller or independent pharmacies, particularly in communities with high need but low public health resource. Second, while stocking naloxone is a necessary requirement for dispensing it, this study found that it was not a sufficient one—we did not, based on our theoretical modeling, identify any single factor that might be sufficient. Third, this study did not address the broader question of what is sufficient to meet the need. It may be the case that stocking naloxone in chain pharmacies and dispensing it from around one-quarter of pharmacies is sufficient to address OOD in this state (Indiana), but it may also be the case that it is insufficient. We recommend studies examine this 'threshold' of access, akin to Bird et al.'s evaluation of Scotland's national naloxone program (2015).

This study is subject to a number of limitations. First, the response rate of 33.4% is adequate but does not preclude the possible introduction of non-response bias. At the same time, differentiation in responses between standard and rigorous recruitment procedures for a survey may not substantively affect findings (Keeter et al., 2006). Second, sample size requirements for logistic regression are complex – Peduzzi et al.'s Monte Carlo study of events per variable (EPV) for binary logistic regression found 10 EPV to be the point at which few adverse statistical effects would be observed (Peduzzi et al., 1996). Our model for naloxone dispensing had slightly lower EPV than suggested (7*10)/.2–or 297 minimum subjects. To attenuate this concern, we checked a version of the dispensing model with 6 predictors (removing the independent variable with the highest correlation with another variable), which would have a minimum requirement of 254 subjects. While the removal of the variable slightly reduced correct classification (3.0% versus 4.5% of dispensing pharmacists), no other statistical issues were observed, so we retained the original model. Third, our assessment of the standing order was based on managing pharmacist perception of the standing order's effect; a concrete assessment of the order's effect would require a different study type, though managing pharmacists are among those most qualified to describe the effects of the order on pharmacy practice. As there was, to our knowledge, no study conducted in Indiana regarding naloxone stocking and dispensing before standing order enactment, this study may be the next best measure of the policy impact on pharmacy behavior, at least for chain pharmacies with more than 1 full-time pharmacist. Finally, logistic regression greatly depends on the theoretical orientation and variables utilized. Thus, this paper should not be taken to indicate that nothing effectively explains managing pharmacist naloxone dispensing behavior, but rather that we may not have selected or identified the specific factors associated with it.

5. Conclusion

Access to naloxone appears to have more to do with structural aspects, namely standing order policies that facilitate stocking by chain pharmacies with more than 1 full-time pharmacist. Factors predicting dispensing, however, continue to elude. Understanding both stocking and dispensing by community pharmacists will clarify just how community pharmacies can and are contributing to the health of PWID during these challenging times.

Role of funding source

Nothing declared.

Contributors

Meyerson, Agley, Shannon, Ryder, Ritchie and Gassman conceived of the study and developed the instrument. Meyerson obtained funding for the study and directed all aspects of the study. Agley and Shannon gathered the data. Agley, Jayawardene, Shannon, Davis and Meyerson conducted the data analysis. Meyerson led the manuscript development. Meyerson, Hoss, Jayawardene and Agley revised the manuscript. All authors contributed to and approved the submitted and revised manuscript.

Conflict of interest

All authors declare no conflict of interests to report.

Acknowledgements

This study was funded in part by the Indiana Clinical and Translational Sciences Institute by Award Number UL1TR001108 from the National Institutes of Health, National Center for Advancing Translational Sciences, Clinical and Translational Sciences. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. It was also funded in part by the Indiana University School of Public Health-Bloomington Faculty Research Grant Program.

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Appendix I-12

ACP Journals

Original Research | 1 January 2013

Annals of Internal Medicine

Cost-Effectiveness of Distributing Naloxone to Heroin Users for Lay Overdose Reversal

Phillip O. Coffin, MD, Sean D. Sullivan, PhD

Author, Article and Disclosure Information

https://doi.org/10.7326/0003-4819-158-1-201301010-00003

This article has been corrected. The original version (PDF) is appended to this article as a Supplement.

Chinese translation

Background:

Opioid overdose is a leading cause of accidental death in the United States.

Objective:

To estimate the cost-effectiveness of distributing naloxone, an opioid antagonist, to heroin users for use at witnessed overdoses.

Design:

Integrated Markov and decision analytic model using deterministic and probabilistic analyses and incorporating recurrent overdoses and a secondary analysis assuming heroin users are a net cost to society.

Data Sources:

Published literature calibrated to epidemiologic data.

Target Population:

Hypothetical 21-year-old novice U.S. heroin user and more experienced users with scenario analyses.

Time Horizon:

Lifetime.

Perspective:

Societal.

Intervention:

Naloxone distribution for lay administration.

Outcome Measures:

Overdose deaths prevented and incremental cost-effectiveness ratio (ICER).

Results of Base-Case Analysis:

In the probabilistic analysis, 6% of overdose deaths were prevented with naloxone distribution; 1 death was prevented for every 227 naloxone kits distributed (95% CI, 71 to 716). Naloxone distribution increased costs by $53 (CI, $3 to $156) and quality-adjusted life-years by 0.119 (CI, 0.017 to 0.378) for an ICER of $438 (CI, $48 to $1706).

Results of Sensitivity Analysis:

Naloxone distribution was cost-effective in all deterministic and probabilistic sensitivity and scenario analyses, and it was cost-saving if it resulted in fewer

overdoses or emergency medical service activations. In a “worst-case scenario” where overdose was rarely witnessed and naloxone was rarely used, minimally effective, and expensive, the ICER was $14 000. If national drug-related expenditures were applied to heroin users, the ICER was $2429.

Limitation:

Limited sources of controlled data resulted in wide CIs.

Conclusion:

Naloxone distribution to heroin users is likely to reduce overdose deaths and is cost-effective, even under markedly conservative assumptions.

Primary Funding Source:

National Institute of Allergy and Infectious Diseases.

NEXT ARTICLE ›

Appendix I-13

BMJ 2013;346:f174 doi: 10.1136/bmj.f174 (Published 31 January 2013)

RESEARCH

Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis

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Abstract

Objective To evaluate the impact of state supported overdose education and nasal naloxone distribution (OEND) programs on rates of opioid related death from overdose and acute care utilization in Massachusetts.

Design Interrupted time series analysis of opioid related overdose death and acute care utilization rates from 2002 to 2009 comparing community-year strata with high and low rates of OEND implementation to those with no implementation.

Setting 19 Massachusetts communities (geographically distinct cities and towns) with at least five fatal opioid overdoses in each of the years 2004 to 2006.

Participants OEND was implemented among opioid users at risk for overdose, social service agency staff, family, and friends of opioid users.

Intervention OEND programs equipped people at risk for overdose and bystanders with nasal naloxone rescue kits and trained them how to prevent, recognize, and respond to an overdose by engaging emergency medical services, providing rescue breathing, and delivering naloxone.

Main outcome measures Adjusted rate ratios for annual deaths related to opioid overdose and utilization of acute care hospitals.

Results Among these communities, OEND programs trained 2912 potential bystanders who reported 327 rescues. Both community-year strata with 1-100 enrollments per 100 000 population (adjusted rate ratio 0.73, 95% confidence interval 0.57 to 0.91) and community-year strata with greater than 100 enrollments per 100 000 population (0.54, 0.39 to 0.76) had significantly reduced adjusted rate ratios compared with communities with no implementation. Differences in rates of acute care hospital utilization were not significant.

Conclusions Opioid overdose death rates were reduced in communities where OEND was implemented. This study provides observational evidence that by training potential bystanders to prevent, recognize, and respond to opioid overdoses, OEND is an effective intervention.

Introduction

Poisoning, nine out of 10 of which are related to drug overdoses,[1] has surpassed motor vehicle crashes to be the leading cause of death by injury in the United States.[2] Overdose is also a major cause of death in Canada,[3] Europe,[4] Asia,[5 6] and Australia.[7] In the United States, increases in fatal overdose since the mid-1990s have been driven by the growth in prescriptions for opioid analgesics[8] and their non-medical use.[9 10] Opioid related emergency department visits and admissions to hospital have increased over the same period.[11] In Massachusetts, since

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Extra material supplied by the author (see http://www.bmj.com/content/346/bmj.f174?tab=related#datasupp)

Map of the 19 communities in Massachusetts
coefficients for covariates in adjusted absolute and relative models of opioid overdose related unintentional deaths
coefficients for covariates in adjusted absolute and relative models of opioid related acute care utilizations
Control models of OEND implementation and ratio of opioid related overdose deaths to cancer deaths
Control models of OEND implementation and ratio of opioid related acute care utilizations to motor vehicle crash acute care utilizations

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2005, annual opioid-related overdose deaths have exceeded motor vehicle deaths.[12]

Strategies have been implemented to deal with opioid overdose. Prescription drug monitoring programs,[13] prescription drug take back days, safe opioid prescribing guidelines, and education programs seek to reduce opioid misuse and/or diversion to people who do not have prescriptions. While these strategies are promising, none has been demonstrated in clinical trials or controlled observational studies to reduce overdose rates. Methadone maintenance treatment[14 15] and supervised injection facilities[16] are strategies associated with decreased fatalities from overdose in controlled studies.

Naloxone is an opioid antagonist that reverses the effects of opioid overdose. Overdose education and naloxone distribution (OEND) programs tackle overdose by educating people at risk for overdose and bystanders in how to prevent, recognize, and respond to an overdose. Participants in the program are trained to recognize signs of overdose, seek help, rescue breathe, use naloxone, and stay with the person who is overdosing. From 1996 through 2010, over 50 000 potential bystanders were trained by OEND programs in the United States, resulting in over 10 000 opioid overdose rescues with naloxone.[17] In March 2012, the United Nations Commission on Narcotic Drugs recognized overdose as a global public health issue that warrants focus by the World Health Organization and member countries, including the use of naloxone for the prevention of opioid overdose.[18] Studies of OEND programs have demonstrated feasibility,[19-22] increased knowledge and skills,[23-26] and a concomitant reduction in fatal overdoses after initiation of OEND.[27 28] A controlled study of OEND and overdose rates has not been completed. Implementation of OEND in Massachusetts in communities with a high burden of opioid overdose created the opportunity to study the impact of OEND on opioid related fatal overdose and acute care hospital utilization rates, using high burden communities with low or no OEND implementation as concurrent controls.

Methods

We conducted an interrupted time series analysis of annual opioid related rates of overdose fatalities and utilization of acute care hospitals comparing communities and years where OEND was implemented with those where it was not. The analysis was conducted at the city/town level. Massachusetts consists of 351 geographically distinct cities and towns (referred to as communities). We included the 19 communities with five or greater opioid related unintentional or undetermined intentional fatal poisonings in each year from 2004 to 2006, which were the years immediately preceding the implementation of OEND.

The Massachusetts OEND program

In 2006-07, two community public health agencies began providing OEND.[20] The Massachusetts Department of Public Health expanded the program to four more organizations in 2007 and two more in 2009. These agencies, which provided HIV education and prevention services to substance users, provided OEND to potential overdose bystanders through trained non-medical public health workers under a standing order from the OEND medical director. Potential overdose bystanders were opioid users at risk for overdose, as well as social service agency staff, family, and friends of opioid users. Training sites included syringe access programs, HIV education drop-in centres, addiction treatment programs, emergency and primary healthcare settings, and community meetings, such as support groups for family members of opioid users.

Training curriculums were initially developed by the Harm Reduction Coalition and the Chicago Recovery Alliance,[19-27] and adapted for nasal naloxone. OEND trainers completed a four hour course, knowledge test, and two trainings of potential bystanders supervised by a master trainer. The training of program participants by OEND trainers were conducted in groups or individually, took as little as 10 minutes for enrollees with substantial pre-existing knowledge and as much as 60 minutes for groups that generated discussion or had enrollees without prior knowledge of overdose, and were tailored to the training setting. Key elements included minimizing the risk of overdose by reducing polysubstance misuse (for example, concomitant alcohol, benzodiazepine, or cocaine), accounting for reduced tolerance after abstinence, and not using alone; recognizing overdose by assessing for unresponsiveness and decreased respirations; and responding to an overdose by seeking help, providing rescue breathing, administering nasal naloxone, and staying with the person until medical personnel arrived or the person recovered. Trainings concluded with enrollees demonstrating proper assembly of the naloxone device and how naloxone should be administered. Naloxone rescue kits contained instructions, two prefilled syringes with 2 mg/2 mL naloxone hydrochloride, and two mucosal atomization devices. Two doses were included in case one dose was not sufficient or if overdose symptoms returned, because the half-life of many opioids is longer than that of naloxone.

Data collection and measures

Fatal opioid overdose rates

For the fatal opioid overdose outcome, we calculated rates of unintentional and undetermined intentional opioid related drug poisonings by community of residence using in-state occurrent deaths from the electronic database maintained by the Massachusetts Registry of Vital Records and Statistics, Massachusetts Department of Public Health. Death certificates on fatal poisonings in Massachusetts are completed through a single centralized, statewide office of the chief medical examiner, where they are required by law to be reported. Opioid related deaths were defined by ICD-10 (international classification of diseases, 10th revision) codes indicating unintentional or undetermined intentional poisoning (X40-X44, Y10-Y14) in the underlying cause of death field and an opioid specific T code of T40.0-T40.4 and/or the narcotic T code T40.6 in any of the multiple cause of death fields. The use of T40.6 to identify opioid related deaths is recommended in jurisdictions where a high proportion of deaths with this code is opioid specific.[29] An unpublished review of 2007 Massachusetts death certificate literals indicated that T40.6 had a positive predictive value of 98% for an opioid related death. Furthermore, 96.7% of unintentional or undetermined intentional deaths by poisoning in Massachusetts in 2007 received at least one ICD-10 code in the range (T36-T50.8), indicating that specific information on agent or class of agent was present on death certificates for nearly all drug related deaths.

Opioid overdose related acute care hospital utilization rates

We used the Massachusetts inpatient hospital and outpatient emergency department discharge databases administered by the Massachusetts Division of Health Care Finance and Policy to quantify acute care hospital inpatient and emergency department discharges associated with opioid poisoning by city or town of residence. Submission of external cause of injury codes (E codes) are required by state regulation on all cases with a

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principle diagnosis of injury or poisoning, ensuring high quality data for state injury surveillance. Cases were defined as discharges having an ICD-9-CM (international classification of diseases, ninth revision, clinical modification) code of one or more of the following opioid related discharge diagnosis or E codes: 965 (.00, .01, .02, .09), E850 (.0, .1, .2). We excluded those cases receiving an E code indicating that the poisoning was the result of intentional self harm, assault, an adverse effect of a drug in therapeutic use, or legal intervention. To avoid duplicate counts with the fatality measure we excluded deaths occurring during the hospital event from this outcome.

Descriptive variables from enrollment and naloxone rescue attempt questionnaires

The Massachusetts Department of Public Health OEND program database included information from program questionnaires collected at both enrollment and whenever an enrollee requested an additional naloxone kit. The completed questionnaires were scanned by form reading software and entered into the program database. At enrollment, zip code of residence, drug use history, and overdose history were collected. We defined users as participants who reported active use or being in treatment or in recovery. Non-users were all other participants, typically social service agency staff, family, and friends of opioid users. A questionnaire was completed when a participant requested a naloxone refill because naloxone had been used during an overdose rescue. Staff were trained to define an overdose when administering the questionnaire as an episode when an individual was unresponsive and had signs of respiratory depression after using substances. We only counted events where participants reported their own overdose rescue attempts if another person administered the naloxone. Self administered naloxone was rarely reported and was not counted as a rescue attempt because a person able to self administer the drug was not considered to be unresponsive. We considered naloxone to be successfully administered if the person's unresponsiveness and respiratory depression improved. Other descriptive variables included the zip code of the place in which the overdose occurred, relationship to the person who overdosed, setting (public or private), number of naloxone doses used, whether naloxone was successful, emergency medical system involvement, rescue breathing, and staying with the person who overdosed.

Independent variables: OEND enrollment rates

To determine the cumulative enrollment rates for the 19 communities with high overdose burdens we used the community of residence based on the zip code of residence on the enrollment questionnaire. We modeled OEND implementation in two ways. Firstly, we categorized OEND implementation into three groups within each year based on the median cumulative enrollment rate (relative model). Groups included community-year strata with no implementation, those below the median (low implementers), and community-year strata with enrollment rates above the median (high implementers). Secondly, to determine if an absolute population density of enrollment was associated with overdose rates, we categorized communities in each year into three categories based on cumulative enrollment rate levels of no implementation, 1-100 per 100 000 population and >100 per 100 000 population (absolute model). In the models we used enrollment cut points of 0, 1-75, >75 and in sensitivity analyses cut points of 0, 1-150, and >150.

Covariates

To account for geographic differences in overdose risk, we adjusted our analyses for demographics. We linearly interpolated community specific data (age, sex, race or ethnicity, poverty) for each year from the community specific 2000[30] and 2010[31] US Census Bureau data.

We used data from the Massachusetts prescription drug monitoring program to adjust for opioid prescriptions to "doctor shoppers," defined as individuals who had schedule II opioid prescriptions from four or more prescribers and filled prescriptions at four or more pharmacies in a 12 month period.[32] We calculated the proportion of schedule II opioid prescriptions dispensed to doctor shoppers per total opioid prescriptions for each community-year stratum.

Inpatient medically supervised withdrawal (detox) results in a period of abstinence that can increase overdose rates,[33 34] whereas engagement in methadone treatment results in decreased rates of overdose.[14] Office based buprenorphine treatment expanded during the study period. To adjust for these three treatment services, we calculated population rates of methadone maintenance, buprenorphine maintenance, and detox events for each community-year stratum using data from the Massachusetts Department of Public Health Bureau of Substance Abuse Services treatment database. Any treatment program licensed by and contracted with the Substance Abuse Services was required to report admission and discharge information.

We accounted for linear trends over the study period by using a time variable T, expressed as 1 for the index year 2002 and increasing in integer increments for each year of the study period.

Statistical analysis

For the interrupted time series we used the annual rates of fatal opioid related overdose and acute care hospital utilization associated with non-fatal opioid overdose by community of residence for the units of analysis. The denominators were the community population based on US Census estimates. Based on the independent variable definitions, we coded individual community-year combinations with an indicator variable denoting "implementation." As in other studies of injury trends[35] and program implementation,[36] we used Poisson regression models to test our hypotheses that those community-year strata with higher implementation would have lower rates. We modeled rates directly with a log-linear statistical model by including counts as the dependent outcome and population at risk as an offset term. We controlled for community level covariates by including them in the model. All hypothesis tests used a significance level (α) of 0.05. We performed regression diagnostics, including quasi likelihood information criteria,[37] to assess goodness of fit. Based on these, we chose first order autoregressive covariance structure to account for the interdependence of repeated measures.

To determine whether our findings were specific to overdose outcomes or due to an unmeasured health system effect, such as healthcare reform, we conducted additional sensitivity analyses. We refit the adjusted Poisson fatal overdose models substituting fatal opioid overdose rates with overdose death to cancer death rate ratios for each community-year stratum using data from the Massachusetts Registry of Vital Records and Statistics. We also refit models substituting acute care utilization rates associated with non-fatal opioid related poisoning with non-fatal opioid related poisoning or non-fatal motor vehicle traffic related injury rate ratio for each community-year stratum.[38] To define cancer deaths we used ICD-10 codes

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C000-C979, representing malignant neoplasms. We defined cases of non-fatal motor vehicle traffic related injury by discharge diagnoses with an ICD-9-CM code of 800-909.2, 909.4, 909.9, 910-994.9, 995.5-995.59, 995.80-995.85 and an E code, E810-E819 (.0-.9), for unintentional motor vehicle traffic crash. All analyses were done using SAS version 9.3.

Results

Table 1⇓ lists the characteristics of the 19 communities in Massachusetts. These make up about 30% of the state population and contribute almost half of Massachusetts' fatal opioid overdoses and acute care hospital utilizations for non-fatal opioid overdose.

Between 18 September 2006 and 31 December 2009 in Massachusetts, 4857 individuals were enrolled in OEND and 545 naloxone rescue attempts reported. Among the 19 communities meeting the study criteria, 2912 individuals were enrolled (table 2⇓) and 327 rescue attempts made (table 3⇓). The experience of witnessing an overdose was common among both users and non-users at enrollment. Users commonly had a personal history of overdose and reported detoxification treatment and incarceration in the past year.

Of 327 rescue attempts using naloxone reported by 212 individuals, 87% (286/327) were reported by users. Most rescue attempts occurred in private settings. The rescuer and the person who overdosed were usually friends. Naloxone was successful in 98% (150/153) of the rescues attempts. For the three rescue attempts where naloxone was not successful, the people who overdosed received care from the emergency medical system and survived.

Among the 19 communities studied, none had any OEND implementation in 2002-05, 7 had some implementation in 2006 (median of 3 enrollees per 100 000 population), 14 had some in 2007 (median of 7 enrollees per 100 000), and all 19 had OEND implementation in 2008-09 (medians of 55 and 142, respectively). Figures 1⇓ and 2⇓ show the unadjusted rates of unintentional opioid related overdose deaths and acute acre utilizations, respectively, categorized by no, low and high implementation.

Adjusted models: OEND implementation and fatal overdose rates

Generally, opioid related death rates were reduced in those communities that implemented OEND compared with community-year strata with no OEND implementation. In the adjusted model based on absolute numbers of enrollments, both the low implementer community-year strata with 1-100 enrollments per 100 000 population (adjusted rate ratio 0.73, 95% confidence interval 0.57 to 0.91) and the high implementer community-year strata with greater than 100 enrollments per 100 000 population (0.54 0.39 to 0.76) had significantly reduced adjusted rate ratios in a dose related fashion compared with communities with no implementation (table 4⇓, for full models see supplementary tables 4a and 4b). In sensitivity analyses, using alternative cut points of 75 enrollments and 150 enrollments per 100 000 population, rate ratios were similar. For the adjusted model that used the median enrollment rates, overdose death rates were reduced, but significantly so only for the low implementer group (0.71, 0.57 to 0.90).

Adjusted models: OEND implementation and opioid related non-fatal acute care hospital utilizations

For non-fatal opioid overdose related acute care hospital utilizations, there was no statistically significant association between the communities based on absolute or relative enrollment rates compared with no implementation (table 5⇓, for full models see supplementary tables 5a and 5b). In sensitivity analyses, rate ratios were similar then alternative cut points of 75 enrollments and 150 enrollments per 100 000 population were used.

Control models

Models in which the opioid related overdose fatality outcome were substituted for the ratio of opioid related overdose death rates over the cancer related death rates had statistically significant associations in a similar pattern to the original models. Thus the associations of OEND implementation with fatal overdose rates occurred independently of any effects related to cancer fatalities (see supplementary table 6). The similar procedure with motor vehicle crash injuries and acute care utilization models showed no association of OEND implementation on rates, independent of motor vehicle injuries (see supplementary table 7).

Discussion

Between 2006 and 2009, Massachusetts overdose education and nasal naloxone distribution (OEND) programs trained thousands of people who use opioids and their families, friends, and social service providers to prevent, recognize, and respond to overdoses, resulting in hundreds of reported rescue attempts. Compared with no implementation, both low and high implementation of OEND were associated with lower rates of opioid related deaths from overdose, when adjusted for demographics, utilization of addiction treatment, and doctor shopping (schedule II opioid prescriptions from ≥4 prescribers and filled prescriptions at ≥4 pharmacies in a 12 month period). These associations were seen independently of effects related to cancer death rates. Rates of opioid related visits to an emergency department and admission to hospital were not significantly different in communities with low or high implementation of OEND.

Strengths and limitations of the study

The major strength of this study was the interrupted time series analysis approach that capitalized on naturally occurring geographic and time controls owing to the broad but variable implementation of OEND in Massachusetts. The study included years 2002-09, yet OEND implementation began in some communities in 2006 and gradually expanded through 2009. Thus the "no implementation" comparison group included all 19 communities for 2002-05 and only those communities with no enrollment in 2006-09. The pre-implementation and post-implementation comparisons (no versus any implementation) hinged on when implementation started in an individual community. Further, we investigated effects among those communities with high and low implementation. When implementation was defined in a relative manner, based on the median implementation rate in each year, there was an association in the expected direction, but there did not seem to be an implementation dose relation with opioid related overdose death rates. Yet when implementation was defined in an absolute manner based on the cumulative number of enrollments per population, there was both an association in the expected

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direction and a dose relation with death rates. A community's absolute enrollment rate had a stronger impact on overdose death rates than the relative enrollment rate. We included both a disease specific mortality and healthcare utilization outcome. We repeated the analyses with substitute outcomes that incorporated unrelated conditions to check if there was some system level effect in how deaths or acute care utilizations were coded that could account for our findings.

Using an observational approach, this study cannot prove definitively that OEND caused a reduction in opioid related overdose death rates. This study had several other limitations to the data available, which we attempted to address. Firstly, the true population of opioid users in each community was not known. To account for this we adjusted analyses for differences in demographics, use of addiction treatment, and proportion of prescriptions to doctor shoppers. Secondly, opioid overdose fatalities may have been misclassified. However, in Massachusetts the medical examiner's office is centralized, with each death certificate processed through the same system. Thirdly, visits to emergency departments and admissions to hospitals associated with opioid poisoning were defined based on administrative discharge codes. Although discharge codes are a blunt measure of cause for utilization, systematic directional misclassification has not been found in other studies.[39] Fourthly, overdoses may have occurred in clusters, which could result in the assumption that spurious events represent a trend. However, this study was conducted over eight years in 19 communities. Fifthly, we created measures of OEND implementation consistent with our conception of how OEND may impact on rates of fatal overdose and acute care utilization, but they have not been validated in other populations. We tested several levels of OEND implementation and found similar patterns of association with opioid related overdose and acute care utilization rates. Lastly, the description of reported overdose rescue attempts was limited to only those rescues reported back to programs, and thus was likely underreported.

Interpretation

This study provides observational evidence that OEND is an effective public health intervention to address increasing mortality in the opioid overdose epidemic by training potential bystanders to prevent, recognize, and respond to opioid overdoses. OEND implementation seemed to have a dose related impact, where the higher the cumulative rate of OEND implementation, the greater the reduction in death rates. While OEND programs should reduce visits to emergency departments and hospital admissions by preventing overdoses in the first place, they may also increase visits by encouraging bystanders to engage the emergency medical system, which is an explicit part of OEND curriculums. This balance of reducing and increasing the use of the emergency medical system may be why no association was found for acute care utilization.

Implications for research, policy, and practice

Some research issues follow from this study. Because OEND targets not only the overdose risk behaviours of the trainee but empowers trainees to intervene in another person's overdose, it makes a fuller impact at the community level rather than at the individual level. Therefore, an individual level prospective clinical trial is unlikely to capture the community level effect of OEND unless it uses a multisite or social network design or measures community level outcomes to account for the network effects and potential contamination between individual participants. It is also important to determine how OEND should be tailored and implemented among different populations to maximize effectiveness. In Massachusetts, similar OEND curriculums have been delivered to heroin users, prescription opioid users, patients in emergency departments, people who are incarcerated, family members, social service providers, police officers, and fire fighters.

This study provides strong support for the public health agency policy and community based organisation practice to implement and expand OEND programs as a key way to address the opioid overdose epidemic. Two features of the Massachusetts OEND programs that supported broad implementation include the use of an nasal naloxone delivery device and the use of a standing order issued by the health department, which allowed non-medical personnel to deliver OEND. These features may enable broader implementation with greater impact as more communities implement OEND.

We thank the Massachusetts OEND program staff, participants, and advocates and the leadership and staff of the Bureau of Substance Abuse Services and Office of HIV/AIDS at the Massachusetts of Department of Public Health for their cooperation and support, including John Auerbach, Andy Epstein, Michael Botticelli, Barry Callis, Grant Carrow, and Leonard Young; Christine Chaisson for her data management support; Jeffrey Samet, Leonard Paulozzi, and Sharon Stancliff for providing input on earlier versions of this manuscript; and Courtney Pierce for managing this project in its early stages. Preliminary data from this study were presented at the American Public Health Association conference on 1 November 2011, Association of Medical Education and Research on Substance Abuse conference on 5 November 2011, and at the US Food and Drug Administration on 12 April 2012.

Contributors: AYW, AO, and HHH developed the original study design and all authors contributed to additional model development. HHH developed the definitions for fatal and non-fatal opioid overdose outcome. EQ managed the data and she and ZX and AO performed data analysis. All authors contributed to data interpretation and had full access to the de-identified dataset in the study and take responsibility for the integrity of the data and accuracy of the data analyses. AYW, MD-S, and AS-A wrote the first draft of the manuscript and all authors contributed to editing. AYW is the guarantor.

Funding: This study was funded by the Center for Disease Control and Prevention- 1R21CE001602 (principal investigator AYW).The funder played no role in study design, data collection, analysis, interpretation of data, writing of the report, or the decision to submit. The researchers had independence from the funder.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: AYW, ZX, EQ, MDS, AS-A, and AO had support from the Center for Disease Control and Prevention grant 1R21CE001602-01 for this study; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the institutional review boards of Boston University Medical Center (H-28736) and the Massachusetts Department of Public Health (249874-3). Because this study used de-identified data previously collected, informed consent was not required.

Data sharing: No additional data available.

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What is already known on this topic

Opioid overdose is a major, expanding cause of preventable death in many countries

Education about overdose and naloxone distribution is an innovative, community based response deployed in many settings that has not been examined in controlled studies

What this study adds

Death rates from opioid overdose were reduced in communities where overdose education and naloxone distribution was implemented compared with not implemented

This provides observational evidence that an overdose education and nasal naloxone distribution program is an effective public health intervention to address the epidemic of fatal opioid overdose

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Accepted: 31 December 2012

Cite this as: *BMJ* 2013;346:f174

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Tables

Table 1| Characteristics of 19 Massachusetts communities* with high opioid overdose burden. Values are percentages unless stated otherwise

Characteristics	Communities (n=19)
2005 population, total	2 055 086
Mean	108 162
Median	87 392
Range	30 236-609 690
Age <18 years	22.4
Male	48.0
Race or ethnicity:	
Hispanic	13.8
White, non-Hispanic	63.9
Black, non-Hispanic	11.9
Other, non-Hispanic	10.1
Below poverty level	16.4
Treatment events per 100 000 people, 2009:	
Inpatient detoxification	630.0
Methadone maintenance	161.8
Stated funded buprenorphine maintenance	41.5
Opioid prescriptions to doctor shoppers†	10.9

*Geographically distinct cities and towns.
†Schedule II opioid prescriptions dispensed to doctor shoppers (individuals with schedule II opioid prescriptions from ≥4 prescribers and filled prescriptions at ≥4 pharmacies in 12 month period) per total opioid prescriptions dispensed.

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Table 2| Characteristics of potential overdose bystanders trained in overdose education and nasal naloxone distribution program in 19 Massachusetts communities*, 2006-09. Numbers are percentages (number/number in group) unless stated otherwise

Characteristics	All enrollees (n=2912)	Users† (n=2007)	Non-users (n=905)
Mean (SD) age (years)	38.1 (12.1)	36.1 (11.1)	42.6 (13.0)
Female and male to female transgender	44.4 (1274/2870)	38.1 (751/1973)	58.3 (523/897)
Race or ethnicity:			
White, non-Hispanic	69.5 (2013/2896)	71.2 (1421/1996)	65.8 (592/900)
Hispanic	16.2 (468/2896)	17.0 (339/1996)	14.3 (129/900)
Black or African American, non-Hispanic	10.5 (305/2896)	8.7 (174/1996)	14.6 (131/900)
Other, non-Hispanic	3.8 (110/2896)	3.1 (62/1996)	5.3 (48/900)
Detox in past year	—	47.3 (950/2007)	NA
Incarceration in past year	—	27.1 (460/1695)	NA
Lifetime history of overdose	—	54.0 (976/1808)	NA
Received naloxone at last overdose	—	60.0 (503/838)	NA
Overdose witnessed ever	73.6 (2036/2767)	80.8 (1571/1944)	56.5 (465/823)
Reported at least one overdose rescue	7.3 (212/2912)	9.2 (184/2007)	3.1 (28/905)

NA=not available.

Denominators less than total number for each group are due to missing information.

*Geographically distinct cities and towns.

†Enrollees who self reported active substance misuse, currently engaged in treatment or in recovery at enrollment.

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Table 3| Overdose rescue attempts reported by bystanders trained in the overdose education and nasal naloxone distribution program in 19 Massachusetts communities*, 2006-09

	% (No/No in group)		
Variables	**All enrollees (n=327)**	**Users† (n=286)**	**Non-users (n=41)**
Status of person who overdosed:			
Friend	69 (216/313)	72 (200/276)	43 (16/37)
Partner or family	16 (49/313)	12 (34/276)	41 (15/37)
Stranger	10 (32/313)	9 (26/276)	16 (6/37)
Self	5 (16/313)	6 (16/276)	0 (0/37)
Overdose setting:			
Private	78 (249/317)	80 (221/277)	70 (28/40)
Public	22 (68/317)	20 (56/277)	30 (12/40)
No of doses used:			
1	48 (149/312)	48 (129/272)	50 (20/40)
2	48 (150/312)	48 (130/272)	50 (20/40)
≥3	4 (13/312)	5 (13/272)	0 (0/40)
Naloxone successful	98 (150/153)	98 (130/133)	100 (20/20)
911 called or emergency personnel present	33 (106/326)	26 (75/285)	76 (31/41)
Rescue breathing performed	38 (123/327)	37 (105/286)	44 (18/41)
Stayed with victim until alert and awake or help arrived	89 (287/321)	90 (253/280)	83 (34/41)

Denominators less than total number for each group are due to missing information.

*Geographically distinct cities and towns.

†Enrollees who self reported active substance use, currently engaged in treatment or in recovery at enrollment.

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Table 4| **Models of overdose education and nasal naloxone distribution implementation and unintentional opioid related overdose death rates in 19 communities* in Massachusetts, 2002-09**

Cumulative enrollments per 100 000 population	Rate ratio	Adjusted rate ratio† (95% CI)	P value
Absolute model:			
No implementation	Reference	Reference	
Low implementation: 1-100 enrollments	0.93	0.73 (0.57 to 0.91)	<0.01
High implementation: >100 enrollments	0.82	0.54 (0.39 to 0.76)	<0.01
Relative model:			
No implementation	Reference	Reference	
Low implementation: <median	0.85	0.71 (0.57 to 0.90)	<0.01
High implementation: >median	1.00	0.78 (0.60 to 1.01)	0.06

*Geographically distinct cities and towns.

†Adjusted for city/town population rates of age under 18, male, race or ethnicity (Hispanic, white, black, other), below poverty level, medically supervised inpatient withdrawal treatment, methadone treatment, Bureau of Substance Abuse Services funded buprenorphine treatment, prescriptions to doctor shoppers (individuals with schedule II opioid prescriptions from ≥4 prescribers and filled prescriptions at ≥4 pharmacies in 12 month period), and year.

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Table 5| Models of overdose education and nasal naloxone distribution implementation and opioid overdose related acute care hospital utilizations in 19 communities* in Massachusetts, 2002-09

Cumulative enrollments per 100 000 population	Rate ratio	Adjusted rate ratio† (95% CI)	P value
Absolute model:			
No implementation	Reference	Reference	
Low implementation: 1-100 enrollments	1.00	0.93 (0.80 to 1.08)	0.4
High implementation: >100 enrollments	1.06	0.92 (0.75 to 1.13)	0.4
Relative model:			
No implementation	Reference	Reference	
Low implementation: <median	0.96	0.90 (0.76 to 1.07)	0.2
High implementation: >median	1.10	1.00 (0.86 to 1.16)	1.0

*Geographically distinct cities and towns.

†Adjusted for city/town population rates of age under 18, male, race or ethnicity (Hispanic, white, black, other), below poverty level, medically supervised inpatient withdrawal treatment, methadone treatment, Bureau of Substance Abuse Services funded buprenorphine treatment, prescriptions to doctor shoppers (individuals with schedule II opioid prescriptions from ≥4 prescribers and filled prescriptions at ≥4 pharmacies in 12 month period), and year.

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Figures

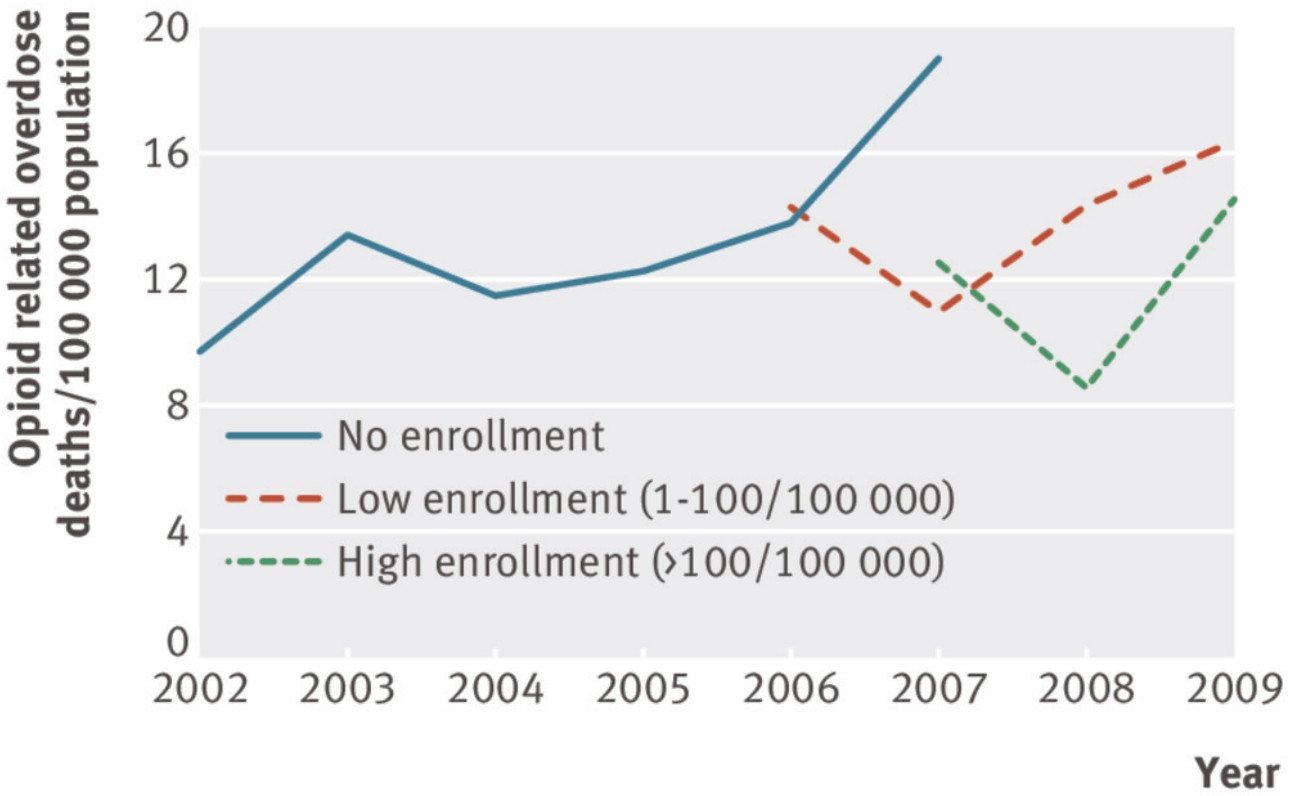

Fig 1 Unadjusted unintentional opioid related overdose death rates in 19 communities with no, low, and high enrollment in overdose education and nasal naloxone distribution program in Massachusetts, 2002-09

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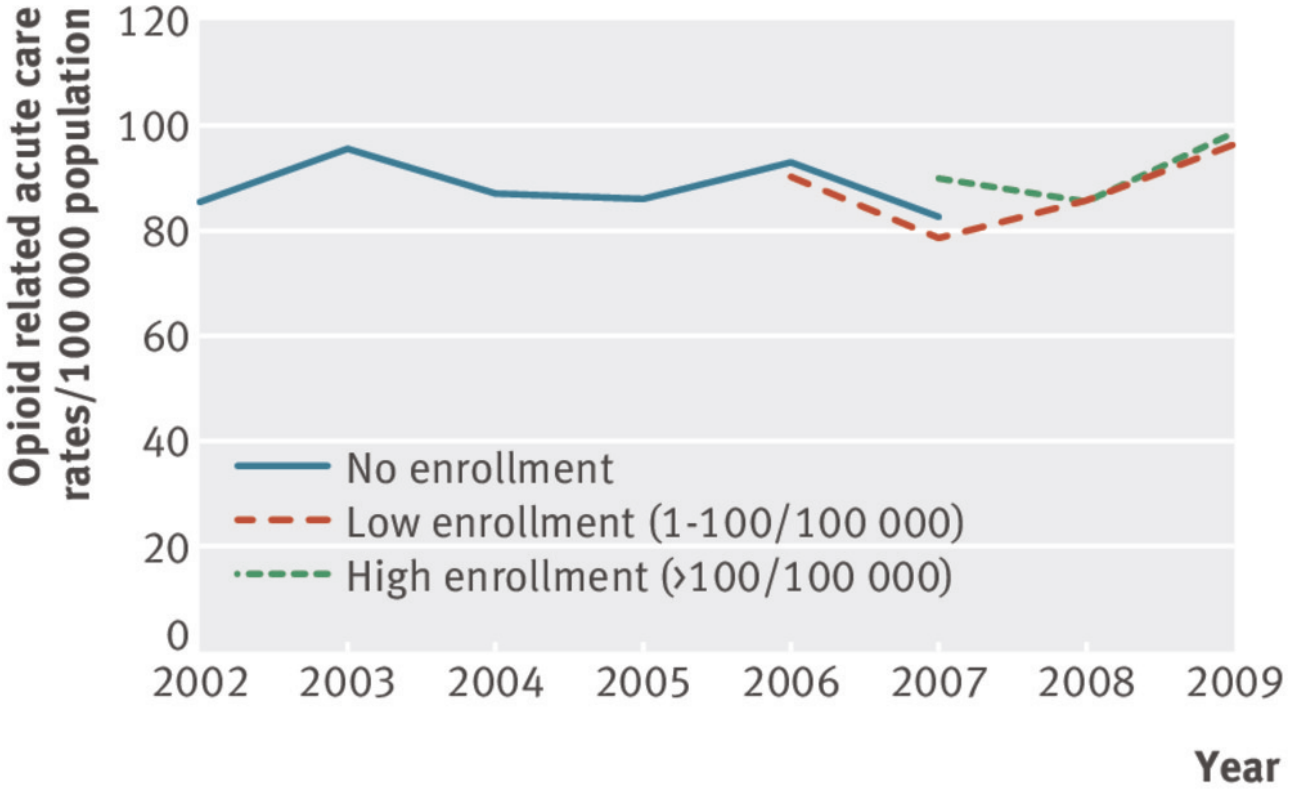
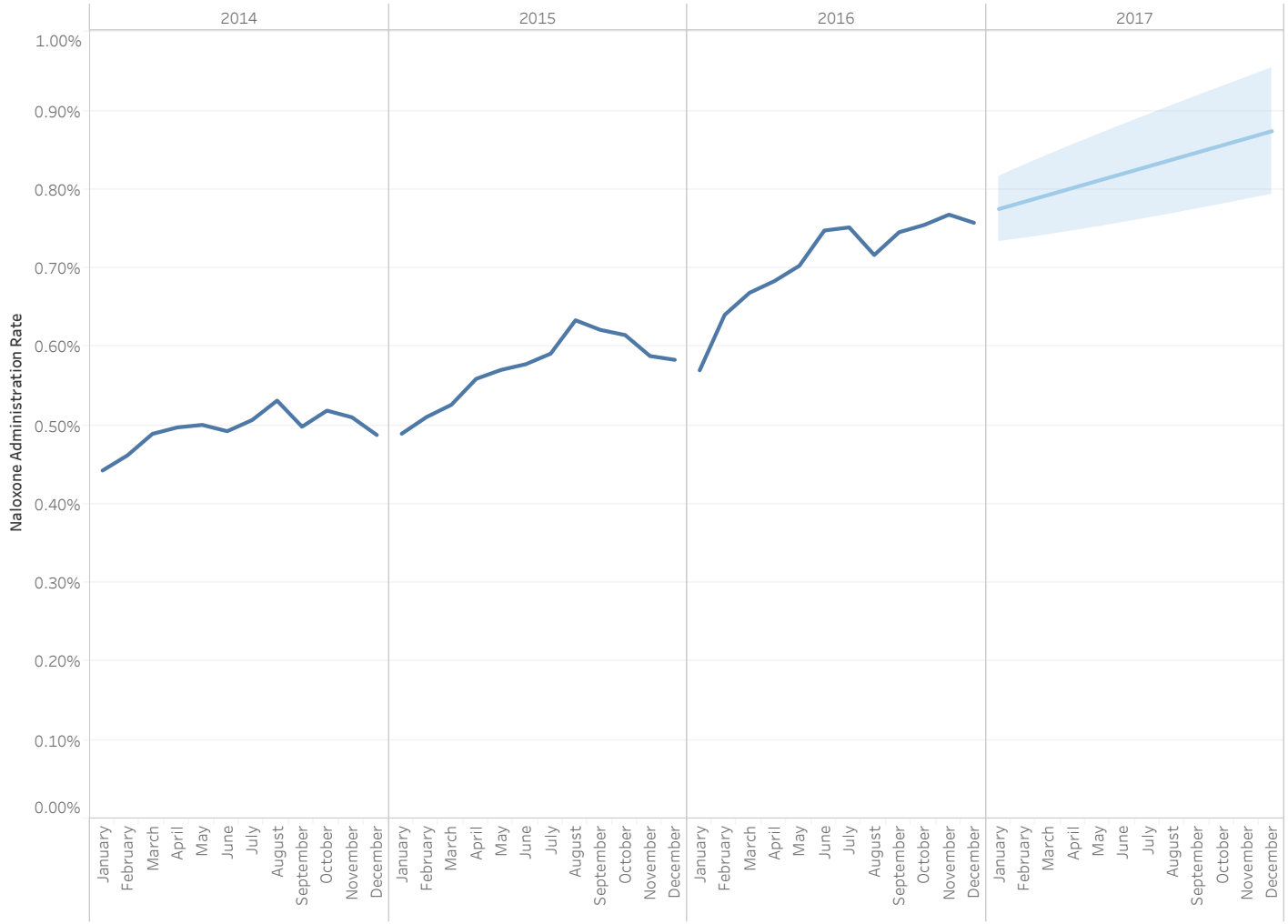


Fig 2 Unadjusted opioid related acute care hospital utilization rates in 19 communities with no, low, and high enrollment in overdose education and nasal naloxone distribution program in Massachusetts, 2002-09

Appendix I-14

Public Naloxone Administration Dashboard

Rate of Naloxone Administration using NEMSIS Activations 2014 to 2016, with projection through 2017



Appendix I-15

FDA STATEMENT

Statement from FDA Commissioner Scott Gottlieb, M.D., on agency's efforts to advance new ways to increase the availability of naloxone as one means for reducing opioid overdose deaths

For Immediate Release:

October 23, 2018

Statement From:

Commissioner of Food and Drugs - Food and Drug Administration
Scott Gottlieb M.D.

With the number of overdose deaths from prescription and illicit opioids doubling from 21,089 in 2010 to 42,249 in 2016, it's critical that we continue to tackle this human tragedy from all fronts – including, and importantly, looking at new ways to increase the availability of naloxone.

This potentially life-saving treatment is a critical tool for individuals, families, first responders and communities to help reduce opioid overdose deaths. We recognize that emergency treatment of known or suspected opioid overdose is an urgent public health priority. And to advance these efforts, there is still a need to improve access to naloxone.

To that end, we're announcing (https://www.federalregister.gov/d/2018-23205) today an upcoming two-day advisory committee meeting in December to solicit input and advice on strategies to increase the availability of naloxone products intended for use in the community.

At this meeting, we'll be asking our external advisors from the FDA's Anesthetic and Analgesic Drug Products and the Drug Safety and Risk Management Advisory Committees to consider various options for increasing access to naloxone. They will help us weigh logistical, economic and harm reduction aspects of different strategies. And we will consider whether naloxone should be co-prescribed with all or some opioid prescriptions to reduce the risk of overdose death.

There is the potential for significant costs and burdens that may be associated with naloxone co-prescribing. These include the direct economic costs to consumers and health systems. They also include practical considerations such as the need for manufacturing volume growth for naloxone, and the risk of drug shortages of this product that could come from a sudden spike in prescribing.

The committee will be asked to evaluate these and other considerations, as part of our effort to consider any potential challenges to wider co-prescribing of naloxone for all or some prescription opioid patients.

December's public meeting builds on the ongoing work that we've undertaken to get this life-saving medication into the hands of those who need it most. When someone overdoses on an opioid, it can be

difficult to awaken the person and breathing may become shallow or stop. This can lead to death if there is no medical intervention.

But, if naloxone is administered quickly, it can counter the overdose effects, usually within minutes. Naloxone can save lives. But it's not a substitute for immediate medical care for a patient who is overdosing on an opioid. Moreover, the person administering naloxone should seek further immediate medical attention on the patient's behalf.

We've been working hard to improve the availability of naloxone products.

In addition to the approval of injectable naloxone for use in a healthcare setting and both prescription auto-injector (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=209862) and intranasal (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=208411) forms of naloxone, which facilitate use by laypersons, we've also released draft guidance for industry (/system/404) to facilitate the development of generic naloxone hydrochloride nasal spray.

We've also made progress on our work to advance the development of an over-the-counter (OTC) naloxone product as a way to promote wider access to this medicine. Although the auto-injector and nasal spray formulations have instructions for use, they don't have the consumer-friendly Drug Facts Label (DFL), which is required for OTC drug products. Before submitting a new drug application or supplement for an OTC drug product, companies need to develop this DFL and conduct the required studies to show that consumers can understand how to use the product without the help of a health care professional. We recognized the important public health opportunity to bring naloxone OTC. So, to further encourage companies to enter this space, the FDA created a model DFL and simple pictogram. And we are in the process of conducting label comprehension testing for this product. This is the first time the FDA has proactively developed this OTC framework for a drug as a way to help activate the advance of OTC products. Using this information, naloxone manufacturers could focus their efforts on final label comprehension testing of how well consumers understand product-specific information that hasn't been already tested on the more general model DFL. We plan to release the results of this work soon.

We plan on discussing the potential development of OTC naloxone at the upcoming meeting. Another topic we plan to discuss is the work that many organizations and local municipalities across the U.S. have done to develop programs for making naloxone available in the community. We hope to glean insight from these efforts to further our own goals at expanding naloxone availability.

We look forward to this important discussion on ways to make naloxone more available to treat opioid overdose. And we are committed working with other federal, state and local officials, health care providers, patients and communities across this country to combat the staggering human and economic toll created by opioid abuse and addiction.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

Appendix I-16

FDA STATEMENT

Statement from FDA Commissioner Scott Gottlieb, M.D., on unprecedented new efforts to support development of over-the-counter naloxone to help reduce opioid overdose deaths

For Immediate Release:

January 17, 2019

Statement From:

With the number of overdose deaths involving prescription and illicit opioids more than doubling over the last seven years to nearly 48,000 in 2017, it's critical that we continue to address this tragedy from all fronts. This includes new ways to increase availability of naloxone, a drug used to treat opioid overdose.

When someone overdoses on an opioid, the person may lose consciousness and breathing may become shallow or stop. This can rapidly lead to death if there's no medical intervention.

However, if naloxone is administered quickly, it can counter the overdose effects, usually within minutes. While the person administering naloxone should also seek immediate medical attention for the patient, the bottom line is that wider availability of naloxone and quick action to administer it can save lives.

Naloxone is a critical drug to help reduce opioid overdose deaths. Prevention and treatment of opioid overdose is an urgent priority. Increased availability of naloxone for emergency treatment of overdoses is an important step. One potential way to improve access to naloxone is to make it available for over-the-counter (OTC) sale. FDA-approved versions of naloxone currently require a prescription, which may be a barrier for people who aren't under the care of a physician or may be ashamed or even fearful of admitting to issues with substance abuse. Having naloxone widely available, for example as an approved OTC product, is an important public health advance, and a need that we've been working on at the FDA.

Although FDA-approved prescription naloxone formulations have instructions for use in product labeling, they don't have the consumer-friendly Drug Facts label (DFL), which is required for OTC drug products. Before submitting a new drug application or supplement for an OTC drug product, companies must develop a DFL and conduct studies to show that consumers can understand how to use the product without the supervision of a health care professional. Some stakeholders have identified the requirement to perform these studies as a barrier to development of OTC naloxone products.

To encourage drug companies to enter the OTC market and increase access to naloxone, the FDA took an unprecedented step: we developed a model DFL with easy-to-understand pictograms on how to use the drug. We also conducted label comprehension testing to ensure the instructions were simple to follow.

This is the first time the FDA has proactively developed and tested a DFL for a drug to support development of an OTC product. We proactively designed, tested and validated the key labeling requirements necessary to approve an OTC version of naloxone and make it available to patients. One of the key components for OTC availability is now in place. In short, we've crafted model labeling that sponsors can use to obtain approval for OTC naloxone and increase its access. This action was part of our broader commitment to addressing the opioid crisis.

Today, we're announcing the results of our work, including posting two model DFLs (one for use with a nasal spray (/media/119743/download) and one for use with an auto-injector (/media/119744/download)) and the supporting FDA review (/media/119745/download). These efforts should jumpstart the development of OTC naloxone products to promote wider access to this medicine. The model DFL contains the information (except for individual product-specific information) that a consumer needs to administer naloxone safely and effectively.

During this period without a FY19 appropriation for the FDA, we've been focused on making sure that we continue critical aspects of our work, to the extent permitted by law. At this time, for products (such as naloxone) that are covered by a user fee program, our review of existing medical product applications and associated policy development regarding our review are funded by limited carryover user fee balances. We'll continue to update the public on how we're approaching our work during the lapse in appropriations.

Consumer comprehension of the model DFL was iteratively tested by an independent research contractor in a prespecified research design involving over 700 participants across a wide range of potential OTC naloxone users. This included people who use heroin; people who use prescription opioids; family and friends of people who use opioids; adolescents; and the general public. An FDA review team not directly involved in the conduct of the study independently reviewed the study report and determined that the comprehension results were satisfactory. Overall, the study demonstrated that the model DFL was well-understood by consumers and is acceptable for use by manufacturers in support of their OTC naloxone development programs. Using this information, naloxone manufacturers can now focus their efforts on final label comprehension testing of how well consumers understand the product-specific information that hasn't been already tested in the model DFL. I personally urge companies to take notice of this pathway that the FDA has opened for them and come to the Agency with applications as soon as possible.

The model DFL comes in two versions. One is for use with a nasal spray and one for use with an auto-injector. But the product-specific instructions in each version are placeholders that have not been tested by the FDA for comprehension or human factors performance. Sponsors can replace these placeholders with their own product-specific information and test it if necessary. Apart from this product-specific information, the model DFL otherwise contains all the key information needed for an untrained bystander to administer naloxone. In designing the model DFL, the FDA team sought input from multiple stakeholders in the addiction care community, as well as from the FDA internal experts, to streamline the DFL to contain only the most critical information, so that it could be easily understood in an emergency. We're grateful to the hundreds of study participants who helped us see this DFL through their eyes, which enabled us to refine the DFL multiple times until we reached a final version. These research participants enabled these efforts.

This work builds on our ongoing efforts to get this life-saving drug into the hands of those who need it most. In addition to the approval of injectable naloxone for use in a health care setting and both prescription auto-injector and intranasal forms of naloxone, which facilitate use by laypersons, we also released draft guidance to advance development of generic naloxone hydrochloride nasal spray.

Additionally, we also held a two-day advisory committee meeting (/advisory-committees/advisory-committee-calendar/december-17-18-2018-joint-meeting-anesthetic-and-analgesic-drug-products-advisory-committee-and-drug) last month to solicit input and advice on strategies to increase the availability of naloxone products intended for use in the community. We asked our external advisors from the FDA's Anesthetic and Analgesic Drug Products and the Drug Safety and Risk Management Advisory Committees to consider various options for increasing access to naloxone.

As part of HHS' ongoing efforts to combat the opioid crisis and expand the use of naloxone, in April 2017, the Department announced its 5-Point Strategy (https://www.hhs.gov/opioids/) to Combat the Opioids Crisis. Those efforts include: better addiction prevention, treatment, and recovery services; better data; better pain management; better targeting of overdose reversing drugs; and better research. In April 2018, Surgeon General VADM Jerome Adams issued an advisory (http://wcms.fda.gov/ucm/resources/wcm/3rdparty/fckeditor/editor/[!--$ssExternalLink('UCM629591')--]) encouraging more individuals, including family, friends, and those who are personally at risk for an opioid overdose to carry naloxone. In December 2018, Adm. Brett P. Giroir, MD, Assistant Secretary for Health and the Secretary's Senior Advisor for Opioid Policy, released guidance (http://wcms.fda.gov/ucm/resources/wcm/3rdparty/fckeditor/editor/[!--$ssExternalLink('UCM629592')--]) for health care providers and patients detailing how naloxone can help save lives.

We're taking many steps to improve availability of naloxone products and we're committed to working with other federal, state and local officials; health care providers; patients; and communities across the country to combat the staggering human and economic toll created by opioid abuse and addiction.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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Related Information

Information about Naloxone (/drugs/postmarket-drug-safety-information-patients-and-providers/information-about-naloxone)

More Press Announcements (/news-events/newsroom/press-announcements)

Appendix I-17

FDA STATEMENT

Statement on continued efforts to increase availability of all forms of naloxone to help reduce opioid overdose deaths

For Immediate Release:

September 20, 2019

Statement From:

Commissioner of Food and Drugs - Food and Drug Administration
Norman E. "Ned" Sharpless MD

Addressing opioid overdose continues to be one of the most urgent public health priorities for the U.S. government and making potentially lifesaving treatments more readily available is one of the top ways we can address this crisis. As we observe Prescription Opioid and Heroin Epidemic Awareness Week, a time when we acknowledge the devastating toll the opioid crisis has inflicted on our country, we felt it was essential to clarify important information about naloxone, an emergency opioid overdose reversal treatment. Naloxone is a critical tool for individuals, families, first responders and communities to help reduce opioid overdose deaths.

Access to naloxone, however, continues to be limited in some communities. There are three FDA-approved forms of naloxone – injectable, auto-injector and nasal spray – and all three currently require a prescription, which can be a barrier for people who aren't under the care of a health care provider or who are apprehensive about admitting to issues with substance abuse. However, in response to the crisis, most states and the District of Columbia have passed laws that allow pharmacists to dispense naloxone under a standing order, which takes the place of an individual prescription. Some states also have given pharmacists direct authority to prescribe and sell naloxone to consumers. Still, many pharmacists may be unaware of the standing orders and direct authority in their states or are unwilling to provide all forms of naloxone to consumers without an individual prescription.

There is also a persistent misunderstanding that the FDA-approved labeling for the injectable form of naloxone, the least expensive option, precludes administration outside a health care setting. This has created confusion among public health officials and community-based organizations about whether the injectable form of naloxone can be used as part of their distribution programs. The FDA-approved product labeling for the three forms of naloxone does not exclude dispensing by pharmacies or community distribution programs. All three forms of naloxone are FDA-approved and may be considered as options for community distribution and use by individuals with or without medical training to stop or reverse the effects of an opioid overdose.

The FDA is working with other federal, state and local officials as well as health care providers, patients and communities across the country to increase availability of all forms of naloxone and combat the toll to communities, individuals and the economy resulting from opioid abuse and addiction. As we continue to confront the opioid crisis, several efforts are underway at the FDA to make naloxone more readily available and accessible.

In April, we approved the first generic naloxone hydrochloride nasal spray (/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-unprecedented-new-efforts-support-development-over), a generic of the brand product, Narcan. The FDA is also granting priority review to all generic applications for products that can be used as emergency treatment of known or suspected opioid overdose. As part of the priority review, sponsors will receive shorter goal dates or standard goal dates with earlier reviewer deadlines; enhanced agency communication with sponsors; and expanded agency engagement, such as pre-submission and mid-cycle meetings.

Making naloxone more widely available in every pharmacy as an approved over-the-counter (OTC) product would also be an important public health advancement – one we have been working on at the FDA. In January, we took an unprecedented step in helping to encourage development of OTC naloxone products (/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-unprecedented-new-efforts-support-development-over). To encourage drug companies to enter the OTC market, the FDA designed, tested and validated the key labeling requirements necessary to approve an OTC version of naloxone. To do this, we developed a model Drug Facts label (DFL) with pictogram instructions so anyone with access to the drug can better understand how to administer it. To ensure the pictograms are easy to understand, we also conducted label comprehension testing with consumers. This was the first time the FDA proactively developed and tested a DFL to support development of an OTC product.

With one of the key components for OTC availability now in place, drug companies can use this information as part of an application to obtain approval for OTC naloxone. We are continuing to work with industry partners who are interested in developing these OTC naloxone products.

The FDA also held a public meeting (/advisory-committees/advisory-committee-calendar/december-17-18-2018-joint-meeting-anesthetic-and-analgesic-drug-products-advisory-committee-and-drug) in December 2018 on various options for increasing access to naloxone, weighing logistical, social and economic aspects of this important issue. There was overwhelming support from meeting participants to remove barriers to obtaining naloxone, particularly OTC naloxone, and to support community activities that expand its availability. As a result, we are currently exploring more ways to increase the availability of all forms of naloxone, such as working with manufacturers to see if shelf-life extensions for naloxone products are possible; conducting additional research on naloxone; and considering situations where co-prescribing of naloxone may be appropriate including possible updated product labeling.

The U.S. Department of Health and Human Services has ongoing efforts to fight the opioid crisis and expand the use of naloxone. In April 2017, the department announced a 5-Point Strategy (https://www.hhs.gov/opioids/) to Combat the Opioids Crisis, including better targeting of overdose reversing drugs. In April 2018, Surgeon General VADM Jerome Adams issued an advisory (https://www.hhs.gov/surgeongeneral/priorities/opioids-and-addiction/naloxone-advisory/index.html) encouraging more individuals, including family, friends and those who are personally at risk for an opioid overdose to carry naloxone. In December 2018, Adm. Brett Giroir, M.D., Assistant Secretary for Health and the Secretary's Senior Advisor for Opioid Policy, released guidance (https://www.hhs.gov/opioids/sites/default/files/2018-12/naloxone-coprescribing-guidance.pdf) for health care professionals and patients detailing how naloxone can help save lives

Ultimately, the goal of increasing access to all forms of naloxone is to make this potentially life-saving treatment available to individuals at risk of an overdose – such as those with a history of overdose or substance use disorder – and those in the community most likely to observe an overdose. The FDA remains committed to using its regulatory authority to address this crisis, working with all our partners to expand the availability of all forms of naloxone, and encouraging prescribers and patients to discuss this topic. All together, these efforts have the potential to put a vital tool for combatting opioid overdose in the hands of those who need it most – friends and family of opioid users, as well as first responders and community-based organizations.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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Appendix I-18

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

FDA Initiative for Drug Facts Label for Over-the-Counter Naloxone

Barbara R. Cohen, M.P.A, Karen M. Mahoney, M.D., Elande Baro, Ph.D., Claudia Squire, M.S., Melissa Beck, B.A., Sara Travis, B.S., Amanda Pike-McCrudden, M.A., Rima Izem, Ph.D., and Janet Woodcock, M.D.

ABSTRACT

BACKGROUND

The opioid crisis highlights the need to increase access to naloxone, possibly through regulatory approval for over-the-counter sales. To address industry-perceived barriers to such access, the Food and Drug Administration (FDA) developed a model drug facts label for such sales to assess whether consumers understood the key statements for safe and effective use.

METHODS

In this label-comprehension study, we conducted individual structured interviews with 710 adults and adolescents, including 430 adults who use opioids and their family and friends. Eight primary end points were developed to assess user comprehension of each of the key steps in the label. Each of these end points included a prespecified target threshold ranging from 80 to 90% that was evaluated through a comparison of the lower boundary of the 95% exact confidence interval.

RESULTS

The results for performance on six primary end points met or exceeded thresholds, including the steps "Check for a suspected overdose" (threshold, 85%; point estimate [PE], 95.8%; 95% confidence interval [CI], 94.0 to 97.1) and "Give the first dose" (threshold, 85%; PE, 98.2%; 95% CI, 96.9 to 99.0). The lower boundaries for four other primary end points ranged from 88.8 to 94.0%. One exception was comprehension of "Call 911 immediately," but this instruction closely approximated the target of 90% (PE, 90.3%; 95% CI, 87.9 to 92.4). Another exception was comprehension of the composite step of "Check, give, and call 911 immediately" (threshold, 85%; PE, 81.1%; 95% CI, 78.0 to 83.9).

CONCLUSIONS

Consumers met thresholds for sufficient understanding of six of eight components of the instructions in the drug facts label for naloxone use and came close on two others. Overall, the FDA found that the model label was adequate for use in the development of a naloxone product intended for over-the-counter sales.

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N Engl J Med 2020;382:2129-36.
DOI: 10.1056/NEJMsa1912403

Timely administration of naloxone can save lives in the event of opioid overdose. Thus, emergency treatment provided by persons who may be at the scene of an overdose plays a crucial role in addressing the ongoing global opioid crisis. World Health Organization guidelines[1] recommend that all persons who are likely to witness an overdose — not only medical professionals but also people who use drugs and their family and friends — have access to naloxone. However, jurisdictional policies related to the availability of naloxone vary across the world, and all too frequently legal and regulatory barriers limit access.[2] In the United States, all 50 states and the District of Columbia have enacted policies to expand access to naloxone, in many instances providing for standing orders and third-party prescribing. Such expanded access allows naloxone to be prescribed both to people who may themselves be at risk for overdose and to people who are in a position to administer naloxone to others. However, both pharmacists and consumers are often either unaware of these options or are aware but associate opioid use and naloxone with stigma, which creates a barrier to purchase.[3] Consequently, many health care professionals and policy makers have called for the availability of over-the-counter naloxone in the United States, which would facilitate direct purchase of the product from the store shelf by anyone, eliminating the gatekeeper.

The regulatory challenge for any industry sponsor seeking approval of an over-the-counter drug product in the United States is to provide evidence through consumer studies that consumers can safely and effectively use the product without guidance from medical professionals. Currently, the over-the-counter drug facts label is the primary means through which instructions for safe and effective use are conveyed to consumers. Potential industry sponsors have previously stated that the requirements for developing a label for over-the-counter naloxone and for assessing the effectiveness of the label through comprehension studies present barriers to bringing naloxone to the over-the-counter market. Our aim was to determine whether the Food and Drug Administration (FDA) could create and test a model label that could be assessed as adequately facilitating appropriate use of naloxone.

As a foundation for the model label, the FDA used the prescribing information for the two prescription products that had been approved for community use as of 2016: Evzio, a prefilled autoinjector, and Narcan, a nasal spray. FDA clinicians, in consultation with experts on the treatment of addiction, distilled the prescribing information for naloxone (which consists of more than 6300 words contained in 18 pages) into what were deemed to be critical elements in instructions for emergency use, limiting the text to the amount that would fit into the format for drug facts labels. The communication experts at the FDA further enhanced label usability by adding white space and boldface type, by "chunking" the information (i.e., breaking up information into small units, or chunks, that make it easier to notice), and by incorporating adjacent pictograms to clarify the stepwise directions for use.[4] FDA social scientists, statisticians, and clinicians designed a label-comprehension study that incorporated best practices from the FDA's *Guidance for Industry: Label Comprehension Studies for Nonprescription Drug Products.*[5]

The research began with a qualitative phase in which the pictograms and language in the label were iteratively revised on the basis of information obtained during in-depth, sequential, one-on-one interviews with 36 participants. This phase was followed by a pilot label-comprehension study involving another 36 participants. These preliminary phases enabled us to craft our label, refine study questions, and determine the sample size for the pivotal study, which is the focus of this article.

Methods

Study Conduct

RTI and Concentrics, the study contractor and subcontractor, respectively, conducted all recruitment and fieldwork, performed prespecified analyses, and prepared a final study report. An independent FDA team then reviewed the data and findings to confirm the results. Under Title 42 Part 11 of the Code of Federal Regulations (CFR), this label-comprehension study did not require registration at ClinicalTrials.gov since it is not regarded as a clinical investigation under Title 21 Part 312.3 of the CFR.

Sample Size and Populations

The pivotal study was designed to include 710 adults and adolescents who met the inclusion

criteria and answered at least one comprehension question (see the data-collection instruments in the Supplementary Appendix, available with the full text of this article at NEJM.org). Three key research subpopulations were identified a priori as representing likely groups of potential over-the-counter naloxone users: adults who had recently used opioids (prescription opioids, heroin, or both) and their family and friends, the general population of adults who had not been screened for opioid use, and the general population of adolescents 15 to 17 years of age who had not been screened for opioid use (see the section on recruitment and data-collection instruments in the Supplementary Appendix). The study plan was to include 430 adults who had used opioids and their family and friends, 140 adults from the general population, and 140 adolescents from the general population (see the section on sample-size justification and handling missing data in the Supplementary Appendix).

The FDA also specified that approximately one third of participants should have limited health literacy, as determined by results on the Rapid Estimate of Adult Literacy in Medicine (REALM) test[6] and the REALM-Teen test.[7] Although the REALM test does not provide an exhaustive assessment of either literacy or health literacy,[8] it is often used by industry sponsors and so provides an important benchmark for this study as compared with similar previous studies.

RECRUITMENT AND DATA COLLECTION

Recruitment of opioid users and their family and friends was conducted through community-based organizations, online advertisements, and participant referral. Recruitment of adults and adolescents in the general population was conducted through market-research sites with the use of their continuously refreshed, large-scale databases, compiled through community outreach. Once participants arrived at the interview site, informed consent was obtained and documented and the REALM test was administered. The one-on-one interview then began. Participants were randomly assigned to receive one of the two drug facts labels that the FDA had developed. The content of the labels was identical except that one was adapted for the use of a nasal spray and one for the use of an autoinjector (Fig. 1). The interviewer then left the room, and the participant had as much time as needed to read the label, at which point the participant called the interviewer back into the room and the interview started. The interview began with a "cognitive walkthrough," a tool that had not been used in previous studies of nonprescription label comprehension and is intended to help the interviewer discern whether participants understand the stepwise sequence involved in the administration of naloxone.[9] During the cognitive walkthrough, participants were asked to imagine that they were in a situation in which they had to use a product on a friend and to state how they would do this, on the basis of the instructions on the label. The interviewer documented the steps mentioned in the walkthrough as well as the order in which they were mentioned. A standard label-comprehension interview then followed, in which participants were asked to apply their understanding of the drug facts label to mainly open-ended questions involving third-party scenarios (see the data-collection instruments in the Supplementary Appendix).

END-POINT DEFINITIONS

Table 1 lists the a priori end points and target thresholds established for label comprehension. For studies of consumer behavior in areas such as label comprehension, the specific target threshold is driven by the magnitude of clinical concern that a labeled statement will not be well understood. Primary end points in our study corresponded to participant understanding of the key steps in naloxone administration as depicted on the label. The most important end point, "call 911," was assessed at a prespecified threshold of 90% for the lower boundary of the confidence interval given the rationale that a person who is overdosing should always receive emergency care from trained medical professionals and that the 911 call needs to be made quickly. The remaining four steps, as well as the composite of steps 1 through 3 (check, give, and call 911), were assessed at a threshold of 85% to denote their slightly lower level of importance as compared with the 911 call. Two messages on the drug facts label (product use for opioid overdose and signs of an overdose) were also determined to be important but less critically so, and these thresholds were set at 80%.

The secondary end points listed in Table 1 encompassed labeled statements that were considered to be not quite as critical to effective use

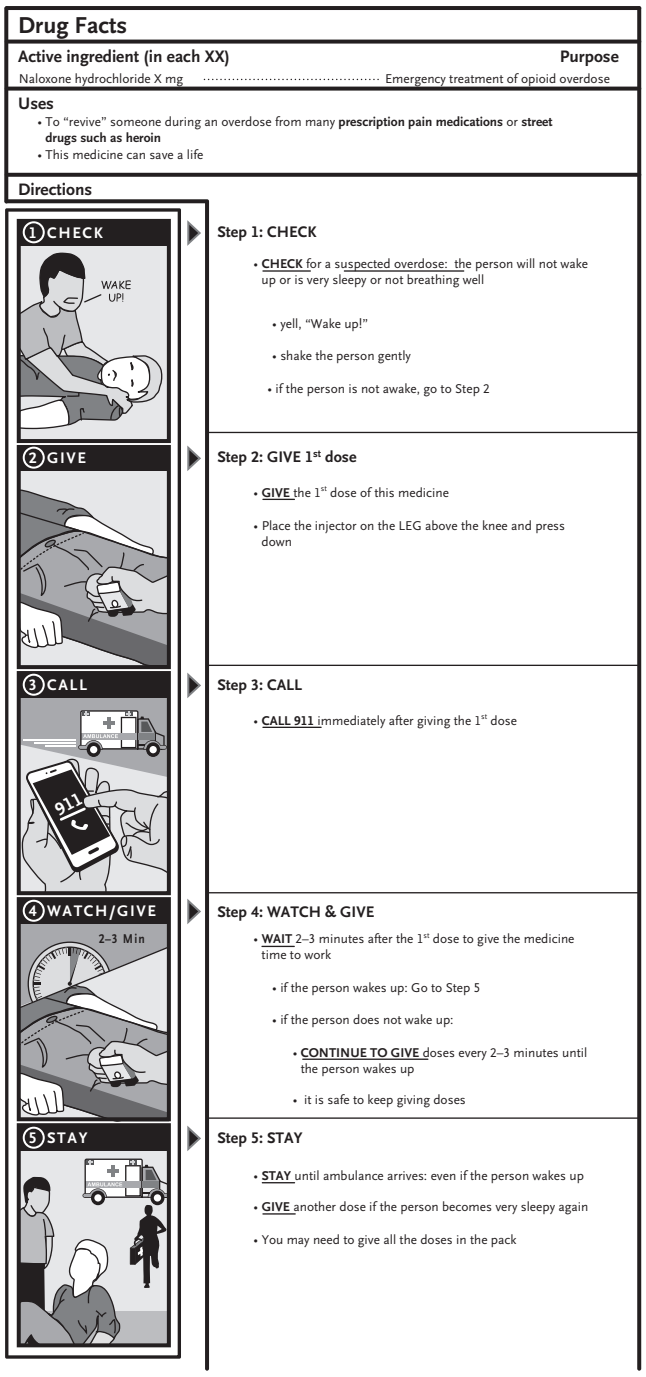

Figure 1. Proposed Food and Drug Administration Drug Facts Label for Naloxone.

The proposed label depicts uses, recommended steps, and warnings regarding the administration of a naloxone injector in response to an opioid overdose. The label for the nasal spray is not shown.

as the primary end points. There were no a priori, prespecified thresholds of comprehension for these end points. The study also included qualitative and exploratory end points regarding the timing between doses, ease of navigation within the label, familiarity with naloxone, and the definition of opioid.

STATISTICAL ANALYSIS

In the primary analysis for primary and secondary end points, the comprehension rate was defined as the number of participants with an overall correct or acceptable response divided by the number of participants in the study population. A correct response was defined as demonstration of a complete understanding of the objective of safe and effective administration of the drug, whereas an acceptable response was defined as demonstration of a sufficient understanding of this objective. In accordance with the statistical analysis plan, estimates of comprehension rate were calculated along with 95% confidence intervals with the use of the Clopper–Pearson exact method for both primary and secondary end points. A primary end point was considered to be met if the lower boundary of the confidence interval was greater than the prespecified target threshold.

Because the step "call 911" was considered to be so important, an analysis of the baseline characteristics of participants whose responses did not reflect an understanding of its importance was conducted. For qualitative and exploratory end points, counts and percentages were reported for each response category. Subgroup analyses that were conducted according to user group, literacy, familiarity with naloxone, and use of opioids were also planned.

RESULTS

STUDY PARTICIPANTS

A total of 720 participants were enrolled in the study; 9 gave consent but did not meet the inclu-

Table 1. Primary and Secondary End Points.*

End Points	Threshold (%)
Primary	
Step 1: Check for a suspected overdose	85
Step 2: Give the first dose of this medicine	85
Step 3: Call 911 immediately	90
Composite of steps 1–3: Check for a suspected overdose, give the first dose of this medicine, and call 911 immediately	85
Step 4: Repeat doses every few minutes until the person is fully awake or until emergency personnel arrive	85
Step 5: Stay with the person until the emergency personnel arrive	85
Product use: Treatment of opioid overdose	80
Signs of overdose: If you think someone used an opioid and the person won't wake up or is not breathing well, these are signs of an overdose	80
Secondary†	
Note that some people may have symptoms when they wake up, such as shaking, sweating, having nausea, or feeling angry	NA
Note that it is safe to keep giving doses	NA
Give another dose if the person becomes very sleepy again	NA
Make sure that the "call 911" step is completed in the appropriate order relative to the other steps	NA
Perform steps 1–5: check for a suspected overdose, give the first dose, call 911 immediately, repeat doses every few minutes, stay with the person until the ambulance arrives	NA

* The target threshold for these end points was set at the specified value for the lower boundary of the 95% confidence interval of the point estimate. NA denotes not applicable.
† No target thresholds were set for the secondary end points.

sion criteria at the time of the interview, and 1 chose not to participate. A total of 710 participants completed the interview. As shown in Table 2, 430 adults who used opioids as well as family members and friends of those who used opioids completed the interview. Most participants who used opioids were recruited from medication-assisted treatment programs in the cities of San Francisco, Chicago, and Charleston, West Virginia; in the Raleigh–Durham area of North Carolina; and in Vance County, also in North Carolina. A total of 280 adults and adolescents from the general population completed the interview. Recruitment was conducted by market-research firms in Tampa, Florida, and in Dallas, Los Angeles, Indianapolis, the Raleigh–Durham area, and New York City. Across all subpopulations, 33.4% had limited literacy. There were similar percentages of male and female participants (51% and 49%, respectively). The mean age was 37.6 years. Participants identified themselves as white (65.4%), black (31.1%), American Indian or Alaska Native (2.8%), Asian (0.7%), or Native Hawaiian or other Pacific Islander (0.7), with the remainder recorded as "other" (see Table 2 for details). In addition, 10% of participants identified themselves as Latino or Hispanic; 84% of all adults had attained at minimum a high school diploma. (See the section on baseline and demographic characteristics in the Supplementary Appendix.)

END POINTS

Among the eight primary end points, six met or exceeded the prespecified target threshold, and the point estimate (PE) scores for seven of the primary end points exceeded 90%. The primary end point that did not meet the 90% threshold was the third step in the sequence: call 911 immediately (PE, 90.3%; 95% confidence interval [CI], 87.9 to 92.4). Analyses of the interview transcripts indicated that in most incorrect re-

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Table 2. Baseline Characteristics of the Participants, Overall and According to Level of Literacy.*

Characteristic	Overall	Normal Literacy	Limited Literacy
Participants — no.	710	473	237
Key research subpopulation — no. (%)			
Opioid user or family or friends of opioid users	430 (60.6)	294 (62.2)	136 (57.4)
Adolescent general population	140 (19.7)	88 (18.6)	52 (21.9)
Adult general population	140 (19.7)	91 (19.2)	49 (20.7)
Race or ethnic group — no. (%)†			
White	464 (65.4)	365 (77.2)	99 (41.8)
Black	221 (31.1)	89 (18.8)	132 (55.7)
American Indian or Alaska Native	20 (2.8)	17 (3.6)	3 (1.3)
Asian	5 (0.7)	5 (1.1)	0
Native Hawaiian or other Pacific Islander	5 (0.7)	4 (0.8)	1 (0.4)
Prefer not to answer	20 (2.8)	14 (3.0)	6 (2.5)
Sex — no. (%)			
Male	359 (50.6)	218 (46.1)	141 (59.5)
Female	351 (49.4)	255 (53.9)	96 (40.5)
Age — yr	37.6±15.6	36.6±14.8	39.7±17.0

* Plus–minus values are means ±SD. For a complete list of baseline characteristics, see Table S1 in the Supplementary Appendix. Participants scoring 61 and above on the REALM test were characterized as having normal literacy and those scoring 60 and below as having limited literacy. Scores of 60 or lower correspond to a seventh- or eighth-grade reading level or lower.
† Race or ethnic group was reported by the participants. Multiple responses were allowed.

sponses, participants stated that the respondent would call 911 but did not state that they would call immediately after giving the first dose. Common reasons for incorrect responses included statements that they would call 911 only if the person did not wake up, if the person did wake up, or after waiting to see if the dose worked (44 participants for all such responses). An additional 25 participants did not mention calling 911 at all. Participants with lower comprehension were more likely to have limited literacy, to have educational attainment below the high school level, to be black, or to be unfamiliar with naloxone.

The primary end point that did not meet the 85% target threshold was the composite of the first three steps (PE, 81.1%; 95% CI, 78.0 to 83.9). Among the 134 participants who had an incorrect response, the reasons that were unrelated to "call 911" included not mentioning checking the person at all (18 of 134 [13.4%]), not mentioning administering a dose (13 of 134 [9.7%]), and mentioning administering a dose before checking the person (7 of 134 [5.2%]). The FDA was intentionally conservative with regard to the coding of the end points involving the 911 call. For example, if a participant did not explicitly state that he or she would call 911 and instead voiced the passive assumption that 911 had been called, the answer was still coded as being incorrect.

Results for the secondary end points are shown in Table 3. The results indicate that the messages were well understood by the participants, with PEs exceeding 80% for all secondary end points except the composite score for reporting all five steps correctly, which was somewhat lower (PE, 74.6%; 95% CI, 71.3 to 77.8).

For the qualitative and exploratory end points, 675 (95.1%) mentioned waiting 2 to 3 minutes between doses; only 23 (3.2%) did not mention a time period, whereas 9 (1.3%) referenced 1.5 to 4 minutes, "a few minutes," or "a couple of minutes." There were 591 participants (83.2%) who reported that the label was easy to navigate; only 5 participants (0.7%) mentioned having trouble

Table 3. Participant Comprehension of Primary and Secondary End Points.*

End Point	% (95% CI)
Primary	
Step 1: Check for a suspected overdose	95.8 (94.0–97.1)
Step 2: Give the first dose	98.2 (96.9–99.0)
Step 3: Call 911 immediately	90.3 (87.9–92.4)
Composite of steps 1–3	81.1 (78.0–83.9)
Step 4: Repeat doses every few minutes	93.8 (91.8–95.5)
Step 5: Stay with the person	91.1 (88.8–93.1)
Use for treatment of opioid overdose	96.5 (94.0–97.7)
Signs of overdose	94.5 (92.6–96.1)
Secondary	
Some people may have symptoms when they wake up	82.4 (79.4–85.1)
It is safe to keep giving doses	95.6 (93.9–97.0)
Another dose should be given if the person becomes very sleepy again	92.3 (90.0–94.1)
The "call 911" step is completed in the appropriate order	85.2 (82.4–87.7)
Performance of steps 1–5	74.6 (71.3–77.8)

* The total number of participants in the study was 710. One participant did not answer all questions, and the missing responses were scored as incorrect, in accordance with the statistical analysis plan.

locating information, only 14 participants (2.0%) mentioned having confusion regarding words, and just 5 participants (0.7%) mentioned having confusion regarding pictograms. Approximately half of participants (379, or 53.4%) reported awareness of naloxone before the study, with just under one third (213, or 30%) stating that they or someone they knew had previously used naloxone.

Participants provided varying responses when asked to define "opioid." The majority did understand the type of overdoses for which naloxone is effective. It appears that the word "opioid" is not universally understood, even by people who use opioids, although most understood the general concept and definition.

All primary and secondary end points were analyzed according to key research subpopulations, literacy level, familiarity with naloxone, opioid subgroup, and interview site. (See the section on baseline and demographic characteristics in the Supplementary Appendix.) Comprehension was similar across the three key research subpopulations, although the adolescent general population had higher scores on three end points (a composite of steps 1 through 3, the order of the "call 911" step, and the instruction to stay with the person until help arrived) than people who used opioids or their family members or friends who used opioids. Comprehension was lower among participants with limited literacy and similar across the groups of people who used opioids, whether prescribed or unprescribed (i.e., heroin or illicit fentanyl), although there were high levels of participant overlap across these subgroups. Participants familiar with naloxone had higher scores on five end points (giving the first dose, calling 911, safety of continuing to give doses, use of product, and recognition of signs of overdose) than those who were not familiar with naloxone.

DISCUSSION

Overall, comprehension of the model naloxone drug facts label met our predefined criteria for acceptability on six of eight primary end points. Although comprehension of the other two end points did not meet predefined criteria, it was within an acceptable range. Label comprehension is often associated with lower scores in persons with limited literacy, and this study had a sizable subgroup with limited literacy. We did

not control for multiple testing in this evaluation and only mitigated type 1 error inflation by prespecifying a hierarchy of end points (primary vs. secondary).

In studies involving consumer behavior regarding the potential use of over-the-counter drugs, it is often the case that target thresholds for primary end points are closely approximated but not fully met. Industry sponsors are encouraged to scrutinize the data for explanations of the failure to meet the predefined goal that can be subsequently addressed in labeling; overall, the FDA considers benefit in conjunction with risk. In the case of over-the-counter naloxone, since 44 of 69 participants' incorrect responses for the end point "call 911" included mention of calling 911 at some point in the process because of a particular anticipated outcome, and since naloxone is a potentially life-saving treatment, we determined that it was reasonable to consider 88% to be an acceptable lower boundary of the confidence interval. In addition, since the coding of this end point was conservative, reported scores are probably underestimates of true comprehension. If naloxone is administered and most users call 911, we reason that many lives may be saved, and this is far preferable to the alternative of not administering naloxone at all. Moreover, as a result of this finding, we think that industry sponsors should continue to consider additional ways to highlight "call 911" on the label. It should be noted that performance on this end point was similar to that observed in many other successful label-comprehension studies in which the labels were ultimately approved on the basis of the overall assessment of benefit as compared with risk.

Our decision to develop a model drug facts label and the conduct of our study to assess consumer comprehension represent a considerable departure from the typical drug development process, in which the sponsor conducts all testing and comes to the agency for approval. This label performed well in facilitating understanding of the important steps needed in evaluating a person who appears to have overdosed and in administering naloxone. The success of this label-comprehension study has enabled much of the regulatory work needed to secure the over-the-counter availability of naloxone and will be key to leveraging over-the-counter product development as a possible means to increasing access to a life-saving drug. We encourage industry sponsors to use this model label to accelerate development initiatives that will ultimately allow for wider access to naloxone. We also anticipate that state and local governments, as well as community-based organizations, will be able to use the tested model label as a component of their training on naloxone administration.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Appendix I-19

James L. Madara, MD
CEO, EXECUTIVE VICE PRESIDENT
james.madara@ama-assn.org

February 15, 2022

The Honorable Rahul Gupta, MD
Director
White House Office of National Drug Control Policy
1800 G Street, NW
Washington, DC 20503

Dear Director Gupta:

On behalf of the American Medical Association (AMA) and our physician and medical student members, I am writing to urge your support to help increase the availability of naloxone in the nation's pharmacies and in the community at-large. The AMA greatly appreciates that the Office of National Drug Control Policy (ONDCP) already has made increasing access to naloxone a high priority to save lives from an opioid-related overdose. We believe that additional steps are necessary, however, to ensure this life-saving medication is more widely available. Specifically, the AMA strongly encourages action to remove the prescription status of naloxone to make it more available over the counter (OTC) and for purchase and distribution by harm reduction organizations. We strongly support comments recently made by Department of Health and Human Services (HHS) Secretary Xavier Becerra in December that HHS is considering how to make naloxone available OTC. We offer several suggestions below.

The nation's drug overdose epidemic killed more than 100,000 Americans in the last year, according to the U.S. Centers for Disease Control and Prevention (CDC). The CDC, ONDCP, and many others understand that the dangers of illicitly manufactured fentanyl, combined with increasing polysubstance use, make the epidemic more deadly than ever, particularly during the ongoing COVID-19 pandemic. If not for naloxone, tens of thousands of additional Americans would likely have died, which is why we need to remove all barriers to naloxone. We agree with the CDC that "naloxone saves lives—but only if it's readily available when an overdose occurs." **The AMA urges removing the prescription status of naloxone as an essential step to save lives from opioid-related overdose because it will help make naloxone more readily available to patients everywhere.**

Removing the prescription status of naloxone was addressed by the U.S. Food and Drug Administration (FDA) back in 2017. The Deputy Director in the Division of Nonprescription Drug Products said that the final piece the FDA needed for OTC status for naloxone was an application from manufacturers. **The FDA has taken unprecedented steps to develop a model drug facts label, use instructions, and has evaluated the efficacy of those instructions, clearly stating: "We conclude that the results of this study are acceptable to support use of the tested naloxone DFL in the OTC setting."** As the overdose epidemic has worsened, given the FDA's clear guidance there is no moral, medical, or safety-related reason for these life-saving overdose reversal agents to remain locked under prescription regulations.

The AMA has done everything we can to encourage naloxone manufacturers to take additional actions to increase access to low- or no-cost naloxone. Some manufacturers have provided discounts to states or municipalities for their life-saving products. Some manufacturers have given limited amounts of their products to harm reduction organizations for free. These efforts have helped, but they are not enough. The AMA has tried repeatedly to urge naloxone manufacturers to further reduce costs and take actions more consistent with the needs of the drug overdose epidemic, but manufacturers claim they are doing all they can do. The AMA has encouraged manufacturers to submit the necessary application to make naloxone OTC, but they have consistently declined.

A few months ago, we renewed our call for OTC status to manufacturers, including Emergent BioSolutions and Teva (makers of a nasal spray application), and Hikma Pharmaceuticals (makers of a branded nasal application and generic intramuscular (IM) application). A copy of our letter can be found here. In response, some manufacturers claim naloxone is not safe for OTC status. Others claim that their price discounts are sufficient. Some manufacturers have not responded to the AMA at all. We have tried everything we can, but manufacturers need more than the nation's physicians' encouragement—they need your specific urging and advocacy to remove the prescription status of naloxone. That is what the nature of this epidemic needs, and we are confident that your leadership can help us reach that life-saving result.

In addition to manufacturers' intransigence, there are additional barriers facing patients being able to access naloxone behind the counter. These include the high cost for those without health insurance, hesitance to dispense naloxone to a person at risk of overdose, and "persistent stigma" surrounding naloxone, according to public health researchers. This is despite physicians' increased prescribing of naloxone, support for OTC naloxone from the American Pharmacists Association, and pharmacy chains' public support for standing orders. Other barriers include largely absent prominent pharmacy signage promoting naloxone availability, stigma and time pressures that serve as a barrier for some pharmacists, and lack of public education about standing orders.

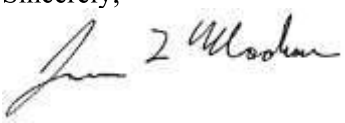
It is also important to note that removing prescription status does not mean that health insurance plans have to stop providing coverage for naloxone. Under the Affordable Care Act, OTC aspirin and certain contraceptives are covered by insurance. Coverage for OTC naloxone could be achieved through legislation, if necessary. It would be better, however, if decisions to continue access to affordable naloxone as a covered benefit were made among employers and payers and pharmacy benefit managers. The AMA will continue to advocate for such coverage as part of a comprehensive strategy to broaden access to naloxone. We further urge all federal programs to continue to provide naloxone via Medicare, Medicaid, the Veterans Health Administration, and the Federal Employees Health Benefits Program. The nation needs this combined strategy of providing naloxone through multiple access points.

In addition to all payers continuing to provide naloxone as a covered benefit, the AMA urges all employers to make sure this occurs because we want to ensure that every person who would benefit from naloxone has access to this life-saving medication for themselves, a family member or friend, or a person whom they might encounter in the community. Removing prescription status simply adds access points for those who may not want to use their insurance and/or ask their pharmacist or physician. **At this point in the nation's overdose epidemic, we must remove all potential barriers to naloxone.**

In sum, the AMA asks your support to: (1) take all necessary steps to make naloxone available and remove its prescription status; and (2) continue the ONDCP's efforts to ensure naloxone is available and affordable for all persons regardless of insurance status and to community-based organizations that expand naloxone access in the communities where it is most needed.

Thank you for your consideration. If you have any questions, please contact Sandy Marks in our Federal Affairs unit at sandy.marks@ama-assn.org or 202-789-4585.

Sincerely,



James L. Madara, MD

Appendix I-20

AMA
AMERICAN MEDICAL ASSOCIATION

James L. Madara, MD
CEO, EXECUTIVE VICE PRESIDENT

james.madara@ama-assn.org

November 4, 2021

Emergent BioSolutions
400 Professionals Drive, #400
Gaithersburg, MD 20879

Dear Stakeholder:

On behalf of the physician and medical student members of the American Medical Association (AMA), I write to request that you submit the appropriate applications to the U.S. Food and Drug Administration (FDA) to make naloxone available as a nonprescription over the counter (OTC) medication. The nation's drug-related overdose and death epidemic is being fueled by increasing levels of illicit fentanyl, fentanyl analogs, and drugs contaminated with illicit fentanyl. Naloxone has proven its efficacy in saving lives from opioid-related overdose. Without this medication, it is likely that tens of thousands more Americans would be dead from an opioid-related overdose. **At this stage in the nation's drug overdose epidemic, there is no valid clinical, public policy, or ethical reason for drug manufacturers to delay OTC applications.**

AMA policy expressly calls on manufacturers to submit OTC applications. Manufacturers of overdose reversal agents can take a drug that has already been approved for prescription use by the FDA and make it available OTC.[1] The FDA has expressly supported making naloxone a nonprescription OTC product, encouraging drug companies to enter the OTC market by granting priority review to all generic applications for drugs that can be used as emergency treatment of known or suspected opioid overdose.[2]

The FDA has also created two model labels for both versions of the drug – one for the nasal spray and one for the auto-injector.[3] In an unprecedented step, the FDA has already designed, tested, and validated these key labeling requirements necessary to approve an OTC version of naloxone.[4] The FDA has even developed a model Drug Facts label with pictogram instructions to ensure anyone with access can effectively administer it.[5] This was the first time the FDA proactively developed and tested a drug label to support OTC development. Any application for an OTC version of naloxone that a manufacturer must complete, therefore, will be easier than most OTC applications since FDA has already completed and approved the labeling portion.

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[2] *Supra* note 6.
[3] *Supra* note 9.
[4] FOOD & DRUG ADMIN., *Statement from FDA Commissioner Scott Gottleib, M.D. on Unprecedented New Efforts to Support Development of Over-The-Counter Naloxone to Help Reduce Opioid Overdose Deaths* (Jan. 17, 2019), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-unprecedented-new-efforts-support-development-over.
[5] *Supra* note 6.

Changing the status of all naloxone products to nonprescription and thereby making them available OTC will strengthen the defensive strategies against the nation's drug overdose epidemic by reducing consumer apprehension. It will also ensure that this opioid-related overdose reversal agent is more widely available.

Last year an unprecedented 93,000 people died in the United States from drug-related overdoses, a rise of nearly 30 percent from 2019.[6] Since 1999, drug-related overdoses have claimed the lives of more than 900,000 people.[7] The stress and anxiety produced by the COVID-19 pandemic led to increased substance use.[8] Coupled with disrupted access to outreach and treatment facilities and increased social isolation, this upsurge of substance use undoubtedly contributed to the increase in overdose deaths.[9] If trends continue at the current pace, drug overdose deaths will surpass the total number of casualties across all major U.S. wars by 2021.[10]

Naloxone has decades of evidence demonstrating that it saves lives. There are three FDA-approved forms of naloxone – injectable, auto-injector, and nasal spray. All three forms currently require a prescription, a condition that limits access for those who are apprehensive to disclose substance abuse issues and for those individuals without health insurance who cannot afford the cost of the product.[11]

States have increased access by adopting pharmacy-based prescription models to increase availability, including a variety of laws that allow prescribers to prescribe naloxone to patients at risk for overdose.[12] Most states permit pharmacies to dispense naloxone under a standing order, which takes the place of an individual prescription from a provider.[13] In addition to these measures, some states have permission for "third-party prescriptions" that authorize doctors and pharmacists to prescribe and dispense naloxone to someone who is not directly at risk for an overdose.[14] **While these actions have laudably tried to expand the availability of naloxone, naloxone remains largely unreachable to those most at risk of overdose**.[15] Our nation needs more readily available, evidence-based tools at its fingertips to save lives from overdose.

The AMA and our physician and student members support and encourage individuals to purchase naloxone without the fear of the "drug addict" stigma associated with the overdose reversal treatment.

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[6] Ahmad FB et al., *Provisional Drug Overdose Death Counts*, NAT'L. CTR. HEALTH STAT. (2021), https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm.
[7] *Wide-Ranging Online Data for Epidemiologic Research (WONDER)*, NAT'L CTR. HEALTH STATS., https://wonder.cdc.gov/ (last updated July 22, 2021).
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[10] *The Rise of Drug Deaths in America*, AM. ADDICTION CTR. (Feb. 23, 2021), https://drugabuse.com/featured/the-rise-of-drug-deaths-in-america/.
[11] FOOD & DRUG ADMIN., *Press Release, Statement on Continued Efforts to Increase Availability of All Forms of Naloxone to Help Reduce Opioid Overdose Deaths* (Sept. 20, 2019), https://www.fda.gov/news-events/press-announcements/statement-continued-efforts-increase-availability-all-forms-naloxone-help-reduce-opioid-overdose.
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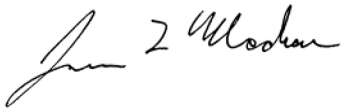
[14] EDU. DEVELOPMENT CTR., *State Naloxone Access Laws*, https://preventionsolutions.edc.org/services/resources/state-naloxone-access-laws (last visited July 27, 2021); *see also* NAT'L. ALL. MODEL STATE DRUG LAWS, *Naloxone Access: Status of State Laws Map (2015),* https://namsdl.org/wp-content/uploads/Naloxone-Access-Status-of-State-Laws-Maps.pdf.
[15] Kendra Walsh & Jeffrey Brathberg, *Plan N: The Case For Over-The-Counter Naloxone*, Health Affairs Blog (July 2, 2021), https://www.healthaffairs.org/do/10.1377/hblog20210630.42921.

The AMA believes that making all naloxone products available OTC and ensuring the privacy of consumers will reduce the number of deaths from opioid-related overdoses. Lives are on the line, and we strongly request your support to engage in these positive efforts to save them by submitting applications to the FDA for OTC naloxone.

Thank you for your consideration. If you have any questions, please contact Daniel Blaney-Koen, JD, Senior Legislative Attorney, AMA Advocacy Resource Center at daniel.blaney-koen@ama-assn.org.

Sincerely,



James L. Madara, MD

Appendix I-21

AMA STATEMENTS

AMA: FDA action on OTC naloxone will save people from overdoses

JAN 17, 2019

Statement attributable to:
Patrice A. Harris, MD, MA
President-elect, chair of the AMA Opioid Task Force
American Medical Association

"The AMA applauds the FDA and Commissioner Gottlieb for today's action to provide labeling that would allow for over-the-counter availability of naloxone, a move that will save people from opioid-related overdose. Naloxone has saved tens of thousands of lives, and the AMA continues to strongly urge physicians to co-prescribe naloxone to patients at risk of opioid-related overdose.

"As called for by AMA policy and ongoing advocacy, today's action should spur efforts by naloxone manufacturers to submit applications for their products to receive over-the-counter status. Doing so would be an important step to save even more lives from a national epidemic."

Media Contact:

Jack Deutsch
ph: (202) 789-7442
jack.deutsch@ama-assn.org

About the American Medical Association

The American Medical Association is the physicians' powerful ally in patient care. As the only medical association that convenes 190+ state and specialty medical societies and other critical stakeholders, the AMA represents physicians with a unified voice to all key players in health care. The AMA leverages its strength by removing the obstacles that interfere with patient care, leading the charge to prevent chronic disease and confront public health crises and, driving the future of medicine to tackle the biggest challenges in health care.

AMA Press Center | Naloxone

Appendix I-22

Shots

PUBLIC HEALTH

To save lives, overdose antidote should be sold over-the-counter, advocates argue

December 14, 2021 · 4:01 AM ET

ANERI PATTANI

FROM KHN

Louise Vincent, executive director of the North Carolina Survivors Union, holds a vial of the overdose reversal drug naloxone. "Almost everyone that comes here is alive because of naloxone," Vincent says.

Aneri Pattani/KHN

Louise Vincent figures her group, the North Carolina Survivors Union, saves at least 1,690 lives a year.

The harm-reduction and syringe service program in Greensboro, N.C., distributes the opioid overdose reversal medication naloxone to people who use drugs. Research suggests this approach is effective, since people who use drugs are most likely to witness an overdose and administer naloxone.

The 1,690 number refers to how many times participants in the Survivors Union reported using the medication between July 2020 and June 2021. But the true number of lives saved could be higher: The program distributed nearly 9,400 doses of naloxone during that time.

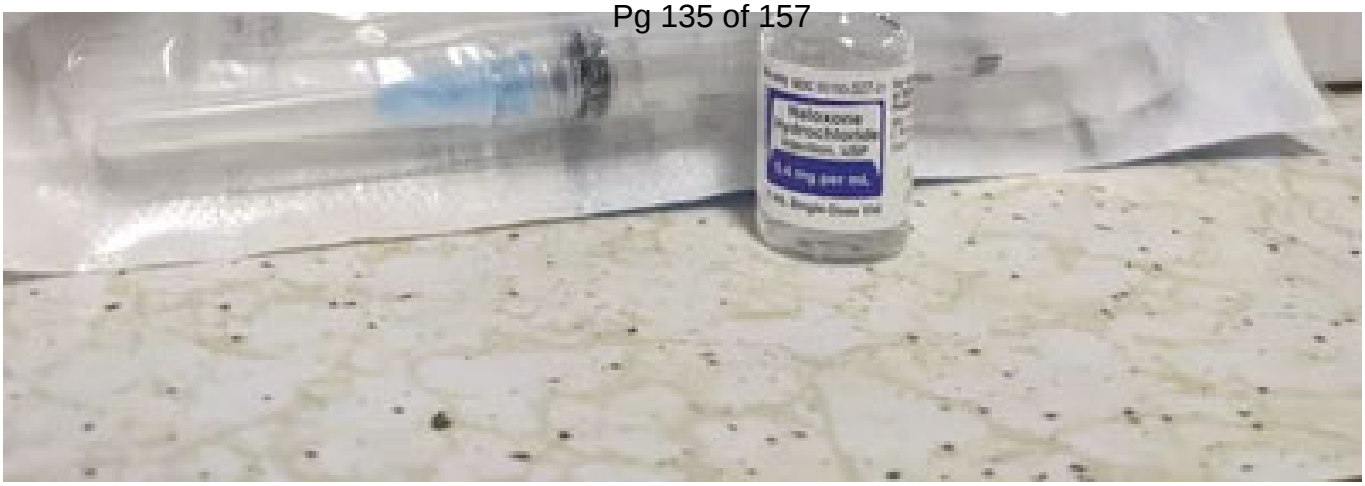
Treatment for addiction is available. For help, call the free and confidential treatment referral hotline (1-800-662-HELP), or visit findtreatment.gov.

Now, as overdose deaths nationwide reach all-time highs, the Biden administration has made increasing access to naloxone a key part of its overdose prevention strategy. It has allotted an unprecedented $30 million in federal funds for harm-reduction groups and announced the creation of a model law that state legislatures can pass to improve access.

But Vincent and her peers say the administration has not addressed their greatest barrier to obtaining the lifesaving medication: naloxone's prescription-only status.

"This designation is the root of all evil," said Nabarun Dasgupta, a scientist at the University of North Carolina's school of public health and co-founder of the Buyers Club, a collective of more than 100 harm-reduction programs in the U.S.

The Food and Drug Administration approved naloxone as a prescription drug to treat opioid overdoses in 1971, when it was only an injectable drug. That remains the cheapest form and the one used most by harm-reduction groups, which have long relied on a deal with Pfizer to buy the medication for less than $5 a dose. However, newer, nasal spray versions of naloxone — including the brand-name drug Narcan, which has a discounted price of about $38 a dose — are available in many police stations, libraries and schools.



Though all 50 states allow individuals to buy naloxone, often known by the brand-name drug Narcan, organizations that order the medication from drugmakers are subject to federal rules that designate the drug as prescription-only. The rules make accessing the lifesaving medication difficult for those at high risk of overdosing.

Aneri Pattani/KHN

All 50 states allow individuals to buy naloxone at the pharmacy without a prescription. States don't have the authority to designate it as an over-the-counter medication, but they've created workarounds — such as a state health official writing one prescription that can be used for every resident. But these workarounds don't apply to organizations that purchase naloxone in bulk from drugmakers.

When a hospital, harm-reduction group or any other organization orders naloxone from pharmaceutical companies, the companies are required to treat naloxone the way the federal government sees it: as a prescription medication, Dasgupta said. As a result, the companies impose a series of requirements on buyers.

For example, an organization that orders naloxone must have a doctor sign for the order, and that doctor must be someone who has not signed for another group. The organization must also have an address that is not a private home to receive shipments, a medical or pharmacy license and the ability to comply with regulations for storing and dispensing the drugs.

Hospitals and health departments can easily fulfill these requirements. But they can be onerous for smaller, grassroots groups, many of which are led by volunteers and operate out of makeshift home or car offices, said Eliza Wheeler and Maya Doe-Simkins, co-founders of the Buyers Club and co-authors of a paper with Dasgupta on this subject.

When these groups can't order naloxone, the people they serve can die, Wheeler and Doe-Simkins said.

Those clients won't necessarily turn to pharmacies. Indeed, as overdose deaths surged in 2020, pharmacy sales of naloxone decreased. The cost of the medication, requirements to show ID, a fear of discrimination from pharmacists and an inability to find a pharmacy that stocks naloxone are all barriers, said West Virginia University researcher Robin Pollini, who studies naloxone distribution.

So harm-reduction groups are calling on the FDA to allow naloxone to be sold over-the-counter so they can order it more easily and distribute it to the people at the greatest risk of overdosing.

The product has long been deemed safe and effective for community use, harm-reduction groups say, even by the FDA. Other advocates have suggested that the Department of Health and Human Services issue an order allowing manufacturers to sell naloxone to organizations buying in bulk without a prescriber's signoff.

"Having more naloxone on the street can only do good. It can't do harm," said Thomas Stopka, an epidemiologist and substance use researcher at Tufts University School of Medicine. "We need to pull out all the stops and consider a bunch of different avenues to address this issue of supply."

The concern was highlighted this year when a manufacturing problem depleted Pfizer's stock of naloxone and the company couldn't fill orders for harm-reduction groups. Hikma, another company that makes naloxone, offered to donate 50,000 injectable doses to the affected groups. But because of naloxone's prescription status and Hikma's associated paperwork requirements, only three harm-reduction programs qualified, Dasgupta said. (Pfizer said that the manufacturing issue has been resolved and that shipments resumed this fall.)

Hana Fields is the co-founder of Stop Harm on Tulsa Streets (SHOTS), a harm-reduction organization in Oklahoma. Since the group's doctor retired in January, SHOTS has relied on naloxone donations from other programs across the state and country.
Rosa Hernandez

In Oklahoma, SHOTS (Stop Harm on Tulsa Streets) didn't qualify for Hikma's donation because the group didn't have a doctor who could sign for its order, co-founder Hana Fields said. The doctor the group had previously worked with retired in January, and SHOTS had yet to find a replacement . Many doctors are worried about liability or simply don't return her calls, she said. In the meantime, SHOTS relies on naloxone donations from other programs.

"The stakes are so high. My friends are dying," said Fields, whose life has been saved by naloxone and who has been in recovery for seven years.

In a statement to KHN, the FDA laid responsibility on the companies making naloxone, saying it has encouraged pharmaceutical manufacturers to apply for over-the-counter designation for years, even doing the legwork to develop consumer-friendly labels that are typically the purview of companies.

"We continue to hope that one or more sponsors will submit an application, as this would be the most direct regulatory path for the FDA to be able to approve a non-

prescription naloxone," the agency said.

But when, or if, that'll happen is unclear.

Pfizer and Hikma told KHN that they do not have current plans to pursue an over-the-counter designation. Emergent BioSolutions, which makes Narcan, said it is "evaluating the potential for OTC naloxone" but warned of "unintended consequences" from the switch, such as insurers no longer covering the cost and consumers having to pay out-of-pocket. (Experts say products typically are cheaper when sold over the counter.)

Harm Reduction Therapeutics, a nonprofit pharmaceutical company, said it plans to apply for an over-the-counter naloxone nasal spray next year, with the goal that it be on shelves in 2023. CEO Michael Hufford said the company will donate most of its product to harm-reduction groups and raise funds to offset the cost to consumers at retail pharmacies. Currently, the bulk of the company's funding comes from Purdue Pharma, the maker of OxyContin.

But advocates say the FDA should make the switch itself.

"We have this lifesaving tool available throughout the whole time of this crisis, and the federal government has just been sitting on its hands," said Leo Beletsky, a professor of law and health sciences at Northeastern University in Boston.

Some pharmaceutical companies in the past have argued that the government doesn't have the authority to designate a prescription drug as over-the-counter, but others point to a statute that allows a drug's prescription status to be removed "when such requirements are not necessary for the protection of the public health." In 1982, the FDA designated an asthma inhaler as an over-the-counter drug without the company's request, though it later rescinded that status because of widespread criticism that the inhalers would be overused.

Meanwhile, harm-reduction organizations, like the North Carolina Survivors Union in Greensboro, see the demand for naloxone daily. Vincent, who runs the program, said cost and regulatory burdens prevent her from ordering naloxone directly. Instead, she

relies on donations from other groups. But she fears the day her group doesn't have enough.

"I can't look someone in the eye and tell them I can't give them medicine that's going to save their lives," Vincent said.

KHN (Kaiser Health News) is an editorially independent newsroom and an operating program of KFF (Kaiser Family Foundation). KFF is an endowed nonprofit organization providing information on health issues to the nation.

harm reduction opioid addiction naloxone narcan

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Appendix I-23

Pharmaceutical & Life Sciences News

Naloxone Dispensing Is Way Up, But Some Areas Still Lag Behind

By Jacquie Lee

Nov. 26, 2019, 5:45 AM

- Health advocates call for over-the-counter version of overdose antidote
- Pharmacists might not know of new gatekeeper role

Naloxone access in some rural counties lags behind the rest of the country despite a massive bump in the overdose antidote's overall dispensing rate.

The disparity shows that there are hitches in the government's efforts to stop overdose deaths. Over the last several years, the administration has pushed for cutting back on the amount of pain pills doctors dole out, education about drug abuse, and funding for rehabilitation.

The "miracle" overdose antidote drug is a big part of the picture. The Surgeon General last year called for "heightened awareness and availability of naloxone,also known as Narcan. Naloxone reverses the effects of a drug overdose and has proven one of the most effective ways to cut back on deaths from overdose.

There are roadblocks to making the life-saving drug widely available in all corners of the country. Pharmacists have been thrust into a new role as gatekeepers for the drug—sometimes without their knowledge or support. And with slim profit margins and over-worked staff, a lot of independent community pharmacies don't have the funds or manpower to order, stock, and educate their customers about naloxone.

"There is still a long way to go to ensure patients who could benefit from naloxone receive it," Gery P. Guy Jr., who helps lead the division of overdose prevention at the Centers for Disease Control and Prevention, said via email. He's especially worried about low dispensing rates in rural counties because they generally have slower emergency response times and don't utilize naloxone enough "in comparison to the overdose burden."

Dispensing in rural counties is lagging compared to metropolitan areas, with rural counties three times more likely to be deemed as "a low-dispensing." According to the CDC's latest research, dispensing is "25 times greater in the highest dispensing counties than the lowest dispensing counties."

The data show federal policy goals aren't being carried out evenly throughout the country. Most states give pharmacists the ability to dispense naloxone without a doctor's prescription. But pharmacists might not be aware the laws exist or are reluctant to give the overdose antidote to their customers.

There is a bright side. Some states that were hardest hit by opioid overdoses have some of the highest county-level dispensing rates, like Florida and Massachusetts, the CDC says. And overall, the number of naloxone prescriptions dispensed increased over 4,000% between 2012 and 2018. States with the lowest dispensing rates included North Dakota, South Dakota, Nebraska, and Iowa.

The main driver of overdoses now are illicit opioids, which can be stronger than prescription drugs. That makes access to naloxone even more critical to prevent overdose deaths, health officials say. In some states, people without a prescription can buy naloxone without first seeing a doctor. They can also carry it on them in case they witness a person overdosing through various state orders. Some nonprofits also give out naloxone in high drug-traffic areas.

The state orders can vary. An over-the-counter naloxone option would mean consistent rules across the country, but so far there is no OTC option.

Why Not Over-The-Counter?

The Food and Drug Administration is encouraging drug manufacturers to make an OTC version of naloxone, which would have to include understandable labels about drug facts and how to administer the product. In January, The FDA took the unprecedented step of laying out sample labels for such a drug. It was the first time the FDA proactively developed and tested a consumer friendly drug label to spur the development of an OTC product. Usually, that's the drugmakers' job

With FDA spelling out the first step, manufacturers for prescription naloxone products can now take that sample label, plug in information for their specific drug, conduct some tests on its efficacy, and submit an application to the FDA to make naloxone for over-the-counter use.

When that application is submitted "it will be a very high priority for the agency to get it approved as quickly as possible," the FDA's Karen Mahoney said in a video.

That was in 2017.

It's hard to pinpoint exactly why there isn't an over-the-counter version now, but the National Association of State Alcohol and Drug Abuse Directors teed up a few reasons in a 2015 report. Naloxone has a "relatively small market value compared to most pharmaceutical products," according to the group. Over-the-counter status might also have "lower price points, decreasing the manufacturer's return on investment" and dampening industry desire to make and sell OTC naloxone.

Taking naloxone isn't like popping an aspirin. FDA says "OTC drugs are defined as drugs that are safe and effective for use by the general public without seeking treatment by a health professional."

That's not exactly the case with naloxone. A member of the general public could use it easily by reading a label. But the people taking it "still need a hospital admission" afterward, David Gortler said. He's a pharmacologist who used to work at the FDA as a medical officer.

The effect of naloxone is jarring. "If they're a pain patient, they'll be in severe withdrawal and in severe pain," he said. For some people, that can cause an irregular heart beat and death if they're seriously addicted. "You give it and call 911 every time."

Ryan Marino does a lot of work with opioid addiction as an emergency doctor and medical toxicologist in Cleveland. He sees an over-the-counter naloxone as one of the best ways to make it more accessible so there aren't "gatekeepers to stand in the way."

Sometimes, he said, health-care providers or members of the general public are hesitant to pass out naloxone freely because they see it as a way of "enabling people."

He described their view in this way: "There's no reason for someone to have it if they're not using heroin."

Other Barriers

Funding for community pharmacies in rural areas presents another barrier. Independent pharmacies work on razor thin margins and can't always pre-order naloxone and have it stocked for when someone asks for it. Rural settings tend to have more independent pharmacies that are "struggling to keep their doors open," said Anne Burns, vice president of professional affairs for the American Pharmacists Association.

"Oftentimes, pharmacists can order it and get it the next day, but sometimes you've lost the patient who might want the naloxone right then," she said.

They also don't have the same resources as chain pharmacies to pour into initiatives on naloxone dispensing, she said. They don't have the money or the networks to offer something similar to Walgreens' step-by-step instructions on how to administer naloxone and find the closest pharmacy to buy it.

Federal guidelines recommend supplying naloxone to people taking a high dose of a prescription opioid. But that's a difficult conversation for pharmacists to initiate with patients.

The efforts to get pharmacists to be "more proactive" in patients' care is laudable but difficult, Burns said. It's about "re-engineering your thought process and trying to have that somewhat difficult conversation with the patient."

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Appendix I-24

FDA Urges Broader Access To Naloxone To Avoid Opioid Overdose Deaths

Kristen Gerencher Contributor ⓘ
Healthcare
I write about chronic diseases, treatments and patients' experiences.

Naloxone, which can reverse symptoms of a life-threatening opioid overdose, is available in three ...
[+] GETTY

The opioid crisis has caused tens of thousands of deaths and exponential suffering. But in an opioid overdose emergency, a life-saving drug called

naloxone can reverse its powerful effects — and is available in many states from your local pharmacist.

While it's not yet available in every community, the U.S. Food and Drug Administration wants more Americans to be able to access naloxone in case they need to administer it to someone who has overdosed. Naloxone comes in a nasal spray, in an auto-injector and in a traditional injectable form, which is the cheapest.

"All three forms of naloxone are FDA-approved and may be considered as options for community distribution and use by individuals with or without medical training to stop or reverse the effects of an opioid overdose," FDA Acting Commissioner Norman "Ned "Sharpless wrote in a statement Sept. 20.

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"Ultimately, the goal of increasing access to all forms of naloxone is to make this potentially life-saving treatment available to individuals at risk of an overdose — such as those with a history of overdose or substance use disorder — and those in the community most likely to observe an overdose."

The FDA says pharmacists may not realize that most states have passed laws or made rules that allow them greater authority to provide naloxone to consumers. The FDA also wants to encourage development of over-the-counter naloxone products by granting priority review to generic applications that can be used to treat opioid overdoses.

“Naloxone I think is the no-brainer of the century. You don’t have [drug] interaction issues and the access is so important to the patients.”

In 2017, more than 47,000 people died from overdoses of prescription and illicit opioids, according to the Centers for Disease Control and Prevention. An opioid overdose typically involves unconsciousness and shallow breathing that can rapidly lead to death without quick medical intervention.

States take action

Ohio, which has been hard hit by the opioid crisis, was among the first states to pass a standing order in 2015 allowing pharmacists to dispense naloxone without a prescription, said Antonio Ciaccia, director of government affairs for the Ohio Pharmacists Association in Columbus.

“Naloxone is I think the no-brainer of the century,” he said. “You don’t have [drug] interaction issues and the access is so important to the patients.”

“The pharmacies believe very strongly if they’re going to be dispensing these very potent medications, they also want to be doing what they can to have the antidote if something goes wrong.”

Even so, after the first year, many Ohio pharmacies have seen their stock of naloxone sit or even expire on the shelves due to lackluster demand, Ciaccia said. That could reflect a sense of shame or stigma patients may feel in asking for it. Slow sales also may be caused by denial, a belief among patients taking opioids that they’re not at risk of overdose or that their children won’t raid the medicine cabinet or accidentally ingest their pills, he said.

“It’s incumbent upon everyone that’s part of the transaction — patient, provider and payer — to make sure these conversations are occurring so if it’s appropriate — that it’s warranted and not wasteful — that the patient walks out with naloxone,“ Ciaccia said.

In California, pharmacists are permitted to dispense naloxone if they have taken a training course and become certified to do so, said Michelle Rivas, vice president of the California Pharmacists Association’s Center for Advocacy, based in Sacramento.

Across the state, “several hundred’” pharmacists are certified to dispense naloxone to patients without a doctor’s prescription, she said, noting the rules were developed by the Board of Pharmacy and the Medical Board of California. Patients, for their part, cannot opt out of counseling with the pharmacist when picking up their naloxone in the Golden State.

> **“There are two polar opposite epidemics right now: There’s massive undertreatment of people suffering with serious illness, but also the opioid epidemic, which is killing people.”**

The expanded authority can help people in rural areas that don’t have clinics and hospitals within driving distance, Rivas said. “Community pharmacists are one of the most easily accessible health-care providers in the state. “

Having naloxone handy when taking opioids is akin to someone with a food allergy carrying an epinephrine auto-injector like EpiPen, she said. “Hopefully they’ll never have to use it, but it’s in their best interest to have it — just like someone with an allergy.”

Another move that could help put naloxone in the hands of people who need it is realigning incentives, Ciaccia said. Pharmacists are paid to fill

prescriptions, and the faster the better, he said.

“If at the end of the day we want more patients who qualify to get naloxone, we need to start building incentives that actually lead to that outcome.”

Help for patients

Naloxone is part of a wider conversation about how to protect patients who are seriously ill and in pain, said Dr. Andrew Esch, a Tampa, Fla.-based internal medicine and hospice and palliative medicine physician and consultant to the Center to Advance Palliative Care.

“There are two polar opposite epidemics right now: There’s massive undertreatment of people suffering with serious illness, but also the opioid epidemic that’s killing people,” Esch said. “We want to make sure we’re getting medication to people who will benefit from it and make sure it’s not getting diverted or misused. “

Doctors and clinicians use tools to screen patients, their caregivers and family members when an opioid is prescribed, and heightened surveillance is an important part of the protocol, he said. When appropriate, it may include shorter supplies of drugs, pill counts, urine toxicology screens, and follow-up appointments, for example.

“We’re always risk-stratifying, trying to pick up on red-flag behavior,” Esch said. “We have to be responsible clinicians. The stakes are too high.”

Another government communication on Sept. 19 highlighted the role of suicide in opioid overdose deaths and the need to prevent it.

Conditions such as depression, addiction and chronic pain can lead to despair, and one study estimated as many as 30% of opioid overdose deaths were suicides, according to a message written by Dr. Joshua Gordon, director of the National Institute of Mental Health, and Dr. Nora Volkow, director of the National Institute on Drug Abuse.

Another study suggested people who misused prescription opioids were 40% to 60% more likely to have thoughts of suicide than those who used them as directed, even after controlling for other conditions, the authors wrote.

For more tips on preventing opioid overdose, check out SAMSHA's Opioid Overdose Prevention Toolkit.

Kristen Gerencher

I am a journalist whose work has appeared in national newspapers and media. Previously, I covered healthcare and personal finance for MarketWatch.com, part of the Wall... **Read More**

Appendix I-25

130 Americans die each day from opioid overdoses. Experts are asking why a lifesaving treatment isn't widely available without a prescription.

Emma Court (/author/emma-court)
Sep. 22, 2019, 04:51 PM

Reuters

- **The prescription medication naloxone can reverse an opioid overdose and has become a key tool in the US's deadly and prolonged opioid crisis.**

- **On Friday (https://www.fda.gov/news-events/press-announcements/statement-continued-efforts-increase-availability-all-forms-naloxone-help-reduce-opioid-overdose), the US Food and Drug Administration highlighted its efforts to increase availability of naloxone, including encouraging companies to create a non-prescription product.**
- **But experts say that the FDA has the power to make naloxone available without a prescription and should do so.**
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An opioid overdose kills **130 Americans each day (https://www.cdc.gov/injury/features/prescription-drug-overdose/index.html)**, on average. So why isn't the opioid overdose antidote naloxone, which is a prescription medication, as widely available as over-the-counter products like Advil and Plan B?

That's a question experts have been asking for years, and they're asking it again now that the US Food and Drug Administration recently **highlighted its work (https://www.fda.gov/news-events/press-announcements/statement-continued-efforts-increase-availability-all-forms-naloxone-help-reduce-opioid-overdose)** to make naloxone more accessible.

The FDA, which regulates medications and other products, has been working to encourage companies to make an over-the-counter naloxone product. Such a treatment would be "an important public health advancement," FDA Acting Commissioner Dr. Ned Sharpless said in a Friday statement.

But experts have also **called on the FDA (https://www.nytimes.com/2017/08/18/opinion/overdose-naloxone-opioids-trump.html)** itself make current naloxone products available without a prescription. One of those experts is Corey Davis, a staff attorney at the National Health Law Program, and he redoubled the call this weekend:

Tweet Embed:
//twitter.com/mims/statuses/1175213035205451776?ref_src=twsrc%5Etfw
The studies are complete. FDA could move one or more products OTC on its own authority, but instead it's decided to wait for a manufacturer to request either an Rx-to-OTC switch or OTC approval for a new product. Meanwhile, 200+ ppl die every day.
Meanwhile, addiction medicine specialist Dr. Stefan Kertesz wrote:

Tweet Embed:
//twitter.com/mims/statuses/1175485362074001408?ref_src=twsrc%5Etfw
Naloxone MUST be made an over the counter med. In our state the Board of Pharmacy opposes community distribution unless a pharmacist directly dispenses the naloxone. They do appear to be right from a regulatory perspective but this locks down access. OTC is the only way. https://t.co/Ef134z5njG (https://t.co/Ef134z5njG)
The US has long been in the throes of a **deadly opioid crisis (https://www.businessinsider.com/new-federal-data-opioid-crisis-pills-dea-us-2019-7?utm_source=markets&utm_medium=ingest)**, with overdose deaths from prescription painkillers as well as heroin and synthetic opioids like fentanyl.

US Surgeon General Jerome Adams has advised Americans who know people at risk of an overdose **to carry naloxone (https://www.businessinsider.com/how-to-use-naloxone-narcan-reverse-overdose-2018-4?utm_source=markets&utm_medium=ingest)**, and said that the rescue medication is a crucial tool, since such overdoses typically happen outside of a medical setting like a hospital.

You should be able to buy naloxone without a prescription, but that doesn't always work out in practice

Because naloxone is so widely recognized as a lifesaving product, many states have taken steps to make it more available.

In most places, you should be able to go to the pharmacy and get naloxone under what's called a "standing order," which works like a blanket prescription for people in that state or area. Certain states also give pharmacists power to **prescribe or sell naloxone (https://naspa.us/resource/naloxone-access-community-pharmacies/)**, the FDA's Sharpless noted. But he also acknowledged the limitations.

"Still, many pharmacists may be unaware of the standing orders and direct authority in their states or are unwilling to provide all forms of naloxone to consumers without an individual prescription," Sharpless wrote in the Friday statement.

A **New York Times investigation (https://www.nytimes.com/2018/04/12/nyregion/overdose-antidote-naloxone-investigation-hard-to-buy.html)** last year found that, of 720 New York City pharmacies that were supposed to sell naloxone without a prescription, only about a third had it in stock and would sell it without a prescription.

And then there is the issue of price. Naloxone can cost up to $150 without insurance, Business Insider has **previously reported (https://www.businessinsider.com/how-to-use-naloxone-narcan-reverse-overdose-2018-4?utm_source=markets&utm_medium=ingest)**, though insurance plans may cap the out-of-pocket costs at around $20. A generic version of the naloxone nasal spray Narcan was **approved by the FDA (https://www.fda.gov/news-events/press-announcements/fda-approves-first-generic-naloxone-nasal-spray-treat-opioid-overdose)** earlier this year, which could help bring down the cost of the medication.

Naloxone should be available as an over-the-counter medication, and the FDA's moves to encourage that are in the right direction, the addiction medicine specialist Kertesz told Business Insider.

He said he was moved to tweet about the issue after being at a New York City event where volunteers were about to hand out pouches containing naloxone.

But issues could still crop up even then, he noted. For instance, if the overdose antidote were made available without a prescription, insurers might stop covering it, exposing consumers to higher costs, he said.

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